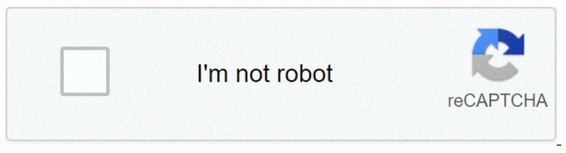

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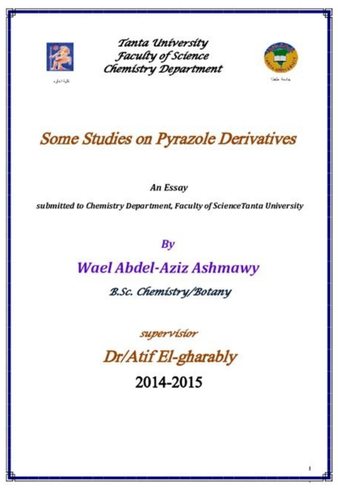
 1. Fustero S., Sánchez-Roselló M., Barrio P., Simón-Fuentes A. From 2000 to Mid-2010: A fruitful decade for the synthesis of pyrazoles. Chem. Rev. 2011;111:6984–7034.



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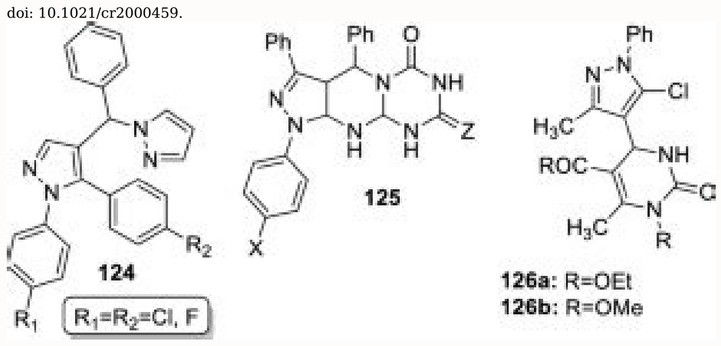
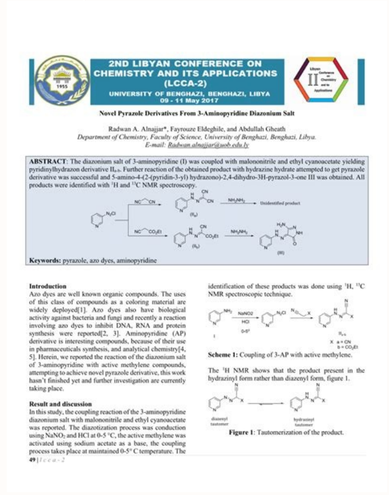
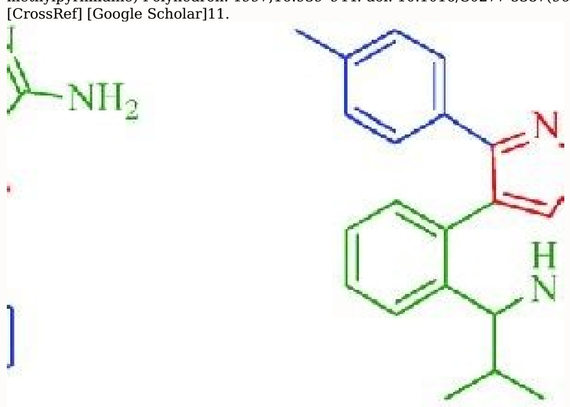


[PubMed] [CrossRef] [Google Scholar]2. Ansari A., Ali A., Asif M. biologically active pyrazole derivatives. New J. Chem. 2017;41:16–41. doi: 10.1039/C6NJ03181A. [CrossRef] [Google Scholar]3. Steinbach G., Lynch P.M., Robin K.S.P., Wallace M.H., Hawk E., Gordon G.B., Wakabayashi N., Saunders B., Shen Y., Fujimura T., Su L.-K., Levin A.B. The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. N.
Engl. J. Med. 2000;342:1946–1952. doi: 10.1056/NEJM200006293422603. [PubMed] [CrossRef] [Google Scholar]4. Uslaner J.M., Parmentier-Batteur S., Flick R.B., Surles N.O., Lam J.S., McNaughton C.H. Dose-dependent effect of CDPPB, the mGluR5 positive allosteric modulator, on recognition memory is associated with GluR1 and CREB phosphorylation in the prefrontal cortex and hippocampus. Neuropharmacology. 2009;57:531–538. doi: 10.1016/j.neuropharm.2009.07.022. [PubMed] [CrossRef] [Google Scholar]5. Friedrich G., Rose T., Rissler K. Determination of lonazolac and its hydroxy and O-sulfated metabolites by on-line sample preparation liquid chromatography with fluorescence detection. J. Chromatogr. B.
2002;766:295–305. doi: 10.1016/S0378-4347(01)00514-X. [PubMed] [CrossRef] [Google Scholar]6. Hampp C., Hartzema A.G., Kauf T.L. Cost-utility analysis of rimonabant in the treatment of obesity. Value Health. 2008;11:389–399. doi: 10.1111/j.1524-4733.2007.00281.x. [PubMed] [CrossRef] [Google Scholar]7. Spitz I., Novis B., Ebert R., Trestian S., LeRoith D., Creutzfeld W. Betazole-induced GIP secretion is not mediated by gastric HCl. Metabolism. 1982;31:380–382. doi: 10.1016/0026-0495(82)90114-7. [PubMed] [CrossRef] [Google Scholar]8. Luttinger D., Hlasta D.J. Antidepressant Agents. Annu. Rep. Med. Chem. 1987;22:21–30.



doi: 10.1016/S0277-5387(96)00346-4. [CrossRef] [Google Scholar]9. Tsutomu K., Toshitaka N. Effects of 1,3-diphenyl-5-(2-dimethylaminopropionamide)-pyrazole [difenamizole] on a conditioned avoidance response. Neuropharmacology.

1978;17:249–256. doi: 10.1016/0028-3908(78)90108-9. [PubMed] [CrossRef] [Google Scholar]10. García-Lozano J., Server-Carrió J., Escrivà E., Folgado J.-V., Molla C., Lezama L. X-ray crystal structure and electronic properties of chlorobis (mepirizole) copper (II) tetrafluoroborate (mepirizole = 4-methoxy-2-(5-methoxy-3-methyl-1H-pyrazol-1-yl)-6-methylpyrimidine) Polyhedron. 1997;16:939–944. doi: 10.1016/S0277-5387(96)00346-4.
[CrossRef] [Google Scholar]11.



Knorr L.
Einwirkung von acetessigester auf phenylhydrazin.
Eur. J.
Inorg. Chem. 1883;16:2597–2599.
doi: 10.1002/cber.188301602194. [CrossRef] [Google Scholar]12. Girish Y.R., Kumar K.S.S., Manasa H.S., Shashikanth S.
ZnO: An Ecofriendly, Green Nano-catalyst for the Synthesis of Pyrazole Derivatives under Aqueous Media. J. Chin. Chem. Soc. 2014;61:1175–1179. doi: 10.1002/jccs.201400170. [CrossRef] [Google Scholar]13. Ohtsuka Y., Uraguchi D., Yamamoto K., Tokuhisa K., Yamakawa T. Syntheses of 2-(trifluoromethyl)-1, 3-dicarbonyl compounds through direct trifluoromethylation with CF3I and their application to fluorinated pyrazoles syntheses. Tetrahedron. 2012;68:2636–2649. doi: 10.1016/j.tet.2012.01.075. [CrossRef] [Google Scholar]14. Gosselin F., O'Shea P.D., Webster R.A., Reamer R.A., Tillyer R.D., Grabowski E.J.J. Highly Regioselective Synthesis of 1-Aryl-3,4,5-Substituted Pyrazoles. Synlett.
2006;19:3267–3270. doi: 10.1055/s-2006-956487. [CrossRef] [Google Scholar]15. Moureu C., Delange R.
Over some Acetylenketone and over a new method to the synthesis of β-Diketones. Bull. Soc.
Chim. Fr. 1901;25:302–313. [Google Scholar]16.
Baldwin J.E., Pritchard G.J., Rathmell R.E. The reactions of diacetylenic ketones with nitrogen nucleophiles; facile preparation of alkynyl substituted pyrimidines and pyrazoles. J. Chem. Soc. Perkin Trans. 1. 2001:2906–2908. doi: 10.1039/b108645f. [CrossRef] [Google Scholar]17. Ji G., Wang X., Zhang S., Xu Y., Ye Y., Li M. Synthesis of 3-trifluoromethylpyrazoles via trifluoromethylation/cyclization of α,β-alkynic hydrazones using a hypervalent iodine reagent. Chem. Commun. 2014;50:4361–4363. doi: 10.1039/C4CC01280A. [PubMed] [CrossRef] [Google Scholar]18. Bishop B.C., Brands K.M., Gibb A.D., Kennedy D.J. Regioselective synthesis of 1,3,5-substituted pyrazoles from acetylenic ketones and hydrazines. Synthesis. 2004;2004:43–52. doi: 10.1055/s-2003-44376. [CrossRef] [Google Scholar]19. Rao V.K., Tiwari R., Chhikara B.S., Shirazi A.N., Parang K., Kumar A. Copper triflate-mediated synthesis of 1,3,5-triarylpyrazoles in [bmim][PF6] ionic liquid and evaluation of their anticancer activities. RSC Adv. 2013;3:15396–15403.
doi: 10.1039/c3ra41830h.
[PMC free article] [PubMed] [CrossRef] [Google Scholar]20. Bhat B.A., Puri S.C., Qurishi M.A., Dhar K.L., Qazi G.N. Synthesis of 3,5-diphenyl-1H-pyrazoles. Synth. Commun. 2005;35:1135–1142. doi: 10.1081/SCC-200054225. [CrossRef] [Google Scholar]21. Huang Y.R., Katzenellenbogen J.A. Regioselective synthesis of 1,3,5-triaryl-4-alkylpyrazoles: Novel ligands for the estrogen receptor. Org. Lett. 2000;2:2833–2836.
doi: 10.1021/ol0062650. [PubMed] [CrossRef] [Google Scholar]22. Ponnala S., Prasad S.D. Iodine-Mediated Synthesis of 2-Arylbenzoxazoles, 2-Arylbenzimidazoles, and 1,3,5-Trisubstituted Pyrazoles. Synth. Commun. 2006;36:2189–2194. doi: 10.1080/00397910600638879.
[CrossRef] [Google Scholar]23. Braibante M.E., Braibante H.T., Da Roza J.K., Henriques D.M., de Carvalho T.L. Synthesis of Aminopyrazoles from α-Oxoketene O,N-Acetals Using Montmorillonite K-10/Ultrasound. Synthesis. 2003;2003:1160–1162. doi: 10.1055/s-2003-39398. [CrossRef] [Google Scholar]24. Rosa F.A., Machado P., Vargas P.S., Bonacorso H.G., Zanatta N., Martins M.A. Straightforward and regiospecific synthesis of pyrazole-5-carboxylates from unsymmetrical enaminodiketones. Synlett. 2008;2008:1673–1678. doi: 10.1055/s-2008-1078482. [CrossRef] [Google Scholar]25. Katritzky A.R., Wang M., Zhang S., Voronkov M.V., Steel P.J. Regioselective synthesis of polysubstituted pyrazoles and isoxazoles. J. Org.
Chem. 2001;66:6787–6791. doi: 10.1021/jo0101407. [PubMed] [CrossRef] [Google Scholar]26. Alberola A., Gonzalez-Ortega A., Luisa Sadaba M., Carmen Sanudo M. [small beta]-Aminoenones in the regioselective synthesis of 1,3,5-trialkylpyrazoles. The influence of the substituents in the mechanism and the regioselectivity of the reaction. J. Chem. Soc. Perkin Trans. 1. 1998;0:4061–4066. doi: 10.1039/a807692h. [CrossRef] [Google Scholar]27.
He S., Chen L., Niu Y.-N., Wu L.-Y., Liang Y.-M. 1,3-Dipolar cycloaddition of diazoacetate compounds to terminal alkynes promoted by Zn (OTf)2: An efficient way to the preparation of pyrazoles. Tetrahedron Lett. 2009;50:2443–2445. doi: 10.1016/j.tetlet.2009.03.030. [CrossRef] [Google Scholar]28.
Gioiello A., Khamidullina A., Fulco M.C., Venturoni F., Zlotsky S., Pellicciari R. New one-pot synthesis of pyrazole-5-carboxylates by 1,3-dipole cycloadditions of ethyl diazoacetate with α-methylene carbonyl compounds. Tetrahedron Lett. 2009;50:5978–5980. doi: 10.1016/j.tetlet.2009.07.152.
[CrossRef] [Google Scholar]29. Jiang N., Li C.-J. Novel 1,3-dipolar cycloaddition of diazocarbonyl compounds to alkynes catalyzed by InCl3 in wate.
Chem. Commun. 2004:394–395. doi: 10.1039/b311763d. [PubMed] [CrossRef] [Google Scholar]30. Qi X., Ready J.M. Copper-Promoted Cycloaddition of Diazocarbonyl Compounds and Acetylides. Angew. Chem. Int. Ed. 2007;46:3242–3244. doi: 10.1002/anie.200700069. [PMC free article] [PubMed] [CrossRef] [Google Scholar]31. Delaunay T., Genix P., Es-Sayed M., Vors J.-P., Monteiro N., Balme G. A Modular Sydnone Cycloaddition/Suzuki-Miyaura Cross-Coupling Strategy to Unsymmetrical 3,5-Bis (hetero) aromatic Pyrazoles. Org. Lett. 2010;12:3328–3331. doi: 10.1021/ol101087j. [PubMed] [CrossRef] [Google Scholar]32. Chen F., Liu F.-M., Shi H., Chen S.-L. A facile access to 1,3,4-trisubstituted pyrazoles via 1,3-dipolar cycloaddition of 3-arylsydnones with α,β-unsaturated ketones. Monatsh. Chem. Chem. Mon. 2013;144:879–884. doi: 10.1007/s00706-012-0901-7. [CrossRef] [Google Scholar]33. Dadiboyena S., Valente E.J., Hamme A.T. A novel synthesis of 1,3,5-trisubstituted pyrazoles through a spiro-pyrazoline intermediate via a tandem 1,3-dipolar cycloaddition/elimination. Tetrahedron Lett.
2009;50:291–294. doi: 10.1016/j.tetlet.2008.10.145. [PMC free article] [PubMed] [CrossRef] [Google Scholar]34. Oh L.M. Synthesis of celecoxib via 1,3-dipolar cycloaddition. Tetrahedron Lett. 2006;47:7943–7946. doi: 10.1016/j.tetlet.2006.08.138. [CrossRef] [Google Scholar]35. Harigae R., Moriyama K., Togo H. Preparation of 3,5-Disubstituted Pyrazoles and Isoxazoles from Terminal Alkynes, Aldehydes, Hydrazines, and Hydroxylamine. J. Org.
Chem. 2014;79:2049–2058. doi: 10.1021/jo4027116. [PubMed] [CrossRef] [Google Scholar]36. Jiang J.-A., Huang W.-B., Zhai J.-J., Liu H.-W., Cai Q., Xu L.-X. 'One-pot' synthesis of 4-substituted 1,5-diaryl-1H-pyrazole-3-carboxylates via lithium tert-butoxide-mediated sterically hindered Claisen condensation and Knorr reaction. Tetrahedron.
2013;69:627–6235. doi: 10.1016/j.tet.2012.11.012. [CrossRef] [Google Scholar]37. Iizuka M., Kondo Y. Palladium-Catalyzed Alkynylcarbonylation of Aryl Iodides with the Use of Mo (CO) 6 in the Presence of tBu3P Ligand. Eur. J.

Org. Chem. 2007;2007:5180–5182. doi: 10.1002/ejoc.200700700. [CrossRef] [Google Scholar]38. Kovacs S., Novak Z.
Copper on iron promoted one-pot synthesis of β-aminoenones and 3,5-disubstituted pyrazoles. Tetrahedron. 2013;69:8987–9893. doi: 10.1016/j.tet.2013.08.047.
[CrossRef] [Google Scholar]39. Dang T.T., Dang T.T., Fischer C., Görls H., Langer P. Synthesis of pyrazole-3-carboxylates and pyrazole-1,5-dicarboxylates by one-pot cyclization of hydrazone dianions with diethyl oxalate. Tetrahedron. 2008;64:2207–2215. doi: 10.1016/j.tet.2007.12.024. [CrossRef] [Google Scholar]40. Lokhande P., Hasanzadeh K., Konda S.G. A novel and efficient approach for the synthesis of new halo substituted 2-arylpyrazolo[4,3-c]coumarin derivatives. Eur. J. Chem. 2011;2:223–228. doi: 10.5155/eurjchem.2.2.223-228.336.
[CrossRef] [Google Scholar]41. Deng X., Mani N.S. Reaction of N-monosubstituted hydrazones with nitroolefins: A novel regioselective pyrazole synthesis. Org. Lett. 2006;8:3505–3508. doi: 10.1021/ol061226v. [PubMed] [CrossRef] [Google Scholar]42.
Deng X., Mani N.S. Base-mediated reaction of hydrazones and nitroolefins with a reversed regioselectivity: A novel synthesis of 1,3,4-trisubstituted pyrazoles. Org. Lett. 2008;10:1307–13010. doi: 10.1021/ol800200j. [PubMed] [CrossRef] [Google Scholar]43. Aggarwal V.K., de Vicente J., Bonnert R.V. A novel one-pot method for the preparation of pyrazoles by 1,3-dipolar cycloadditions of diazo compounds generated in situ. J. Org. Chem. 2003;68:5381–5383. doi: 10.1021/jo0268409.
[PubMed] [CrossRef] [Google Scholar]44. Yadav J., Reddy B.S., Srinivas M., Prabhakar A., Jagadeesh B. Montmorillonite KSF clay-promoted synthesis of enantiomerically pure 5-substituted pyrazoles from 2,3-dihydro-4H-pyran-4-ones. Tetrahedron Lett. 2004;45:6033–6036. doi: 10.1016/j.tetlet.2004.06.031. [CrossRef] [Google Scholar]45. Xie F., Cheng G., Hu Y. Three-component, one-pot reaction for the combinatorial synthesis of 1,3,4-substituted pyrazoles. J. Comb. Chem. 2006;8:286–288. doi: 10.1021/cc050159d. [PubMed] [CrossRef] [Google Scholar]46. Arkhipov V., Garazd M., Smirnov M., Khilya V. Chemistry of Modified Flavonoids. 24. Synthesis of 4-Aryloxy-3-(2-hydroxy-4-hydroxy/alkoxyphenyl) pyrazoles. Chem. Heterocycl. Compd. 2004;40:183–187. doi: 10.1023/B:COHC.0000027889.10448.c1. [CrossRef] [Google Scholar]47.
Sosnovskikh V.Y., Barabanov M., Usachev B. Reactions of 5,7-dimethyl-2-polyfluoroalkyl-8-azachromones with N-nucleophiles.
Russ. Chem. Bull.
2003;52:1758–1767. doi: 10.1023/A:1026000619881. [CrossRef] [Google Scholar]48. Usachev B., Shafeev M., Sosnovskikh V.Y. Synthesis and reactivity of 2-polyfluoroalkylchromene-4(4H)-thiones.
Russ. Chem. Bull. 2004;53:2285–2292. doi: 10.1007/s11172-005-0115-9. [CrossRef] [Google Scholar]49. Sosnovskikh V.Y., Usachev B., Sizov A.Y. 2-Polyfluoroalkylchromones. 14. Synthesis of 4-chloro-3(5)-(2-hydroxyaryl)-5(3)-polyfluoroalkylpyrazoles. Russ. Chem. Bull. 2003;52:508–510. doi: 10.1023/A:1023408327104. [CrossRef] [Google Scholar]50. İlhan İ.Ö., Saripinar E., Akçamur Y. Synthesis of some pyrazole-3-carboxylic acid-hydrazide and pyrazolopyridazine compounds. J. Heterocycl. Chem. 2005;42:117–120. doi: 10.1002/jhet.5570420117. [CrossRef] [Google Scholar]51. Sener A., Kasimogullari R., Sener M., Genç H. Studies on reactions of cyclic oxalyl compounds with hydrazines or hydrazones. 2.
Synthesis and reactions of 4-benzoyl-1-(4-nitrophenyl)-5-phenyl-1H-pyrazole-3-carboxylic acid.
Chem. Heterocycl. Compd. 2004;40:1039–1046. doi: 10.1023/B:COHC.0000046695.00178.79. [CrossRef] [Google Scholar]52. Krishnaiah A., Narsaiah B. A novel approach to the synthesis of 5-trifluoromethyl-3-substituted pyrazoles. J. Fluor. Chem. 2002;115:9–11. doi: 10.1016/S0022-1139(01)00501-2. [CrossRef] [Google Scholar]53. Bisenieks E., Uldrikis J., Duburs G. Reaction of 3,5-carbonyl-substituted 1,4-dihydropyridines with hydrazine hydrate. Chem. Heterocycl. Compd. 2004;40:869–875. doi: 10.1023/B:COHC.0000044569.14048.79. [CrossRef] [Google Scholar]54. Grošelj U., Drobnič A., Rečnik S., Svete J., Stanovnik B., Golobič A., Nina L., Ivan L., Anton M., Simona G.-G. 1,3-Dipolar Cycloadditions to (5Z)-1-Acyl-5-(cyanomethylidene)-imidazolidine-2,4-diones: Synthesis and Transformations of Spirohydantoin Derivatives.
Helv.
Chim. Acta. 2001;84:3403–3417. doi: 10.1002/1522-2675(20011114)84:11<3403::AID-HLCA3403>3.0.CO;2-G. [CrossRef] [Google Scholar]55. Kawase M., Koiwai H., Yamano A., Miyamae H. Regioselective reaction of mesoionic 4-trifluoroacetyl-1,3-oxazolium-5-olates and phenylhydrazine: Synthesis of trifluoromethyl substituted pyrazole and 1,2,4-triazine derivatives. Tetrahedron Lett.
1998;39:663–666. doi: 10.1016/S0040-4039(97)10712-2. [CrossRef] [Google Scholar]56. Simoni D., Rondanin R., Furnò G., Aiello E., Invidiata F.P. Facile synthesis of pyrazoles and pyrroles via thermolysis of tetrazolo[1,5-b]pyridazines, tetrazolo[1,5-a]pyrimidines and tetrazolo[1,5-a]pyridines.
Tetrahedron Lett. 2000;41:2699–2703. doi: 10.1016/S0040-4039(00)00243-4. [CrossRef] [Google Scholar]57. Rykowski A., Branowska D. Ring transformation of 3-halo-1,2,4-triazines with α-chlorocarbanions: A novel route to pyrazoles with sulfonyl, sulfonamido and sulfonyloxy groups. Heterocycles.
1996;10:2095–2098. doi: 10.3987/COM-96-7554. [CrossRef] [Google Scholar]58. Ferfra S., Ahabchane N.H., Garrigues B., Essassi E.M. Nouvelle méthode de synthèse de quinoxalines associées à différents hétérocycles à cinq chaînons. C. R. Acad. Sci. IIC. 2001;4:905–911. doi: 10.1016/S1387-1609(01)01336-6.
[CrossRef] [Google Scholar]59. Dzvinchuk I., Lozinskii M. Hydrazinolytic Recyclization of (Z)-3-Acetyl-2-methyl-2,3-dihydro-1,4-benzodioxin-2-ol. Chem. Heterocycl.
Compd. 2001;37:459–462. doi: 10.1023/A:1017647803950. [CrossRef] [Google Scholar]60. Azev Y.A., Lork E., Gabel D., Duelcks T. New way of the reaction of 1-amino-6,7-difluoro-4-oxoquinolyl-3-ethylcarboxylate with acetoacetone. Mendeleev Commun. 2003;13:184–185.
doi: 10.1070/MC2003v013n04ABEH001797.
[CrossRef] [Google Scholar]61. Pfeiffer W.-D., Dilk E., Rossberg H., Langer P. Synthesis and Reactivity of 3,4-Dimethyl-4H-1,3,4-thiadiazines. Synlett. 2003;2003:2392–2394. doi: 10.1055/s-2003-43342.
[CrossRef] [Google Scholar]62. Guillard J., Goujon F., Badol P., Poullain D. New synthetic route to diaminonitropyrazoles as precursors of energetic materials. Tetrahedron Lett. 2003;44:5943–5945. doi: 10.1016/S0040-4039(03)01301-7. [CrossRef] [Google Scholar]63. Suen Y.F., Hope H., Nantz M.H., Haddadin M.J., Kurth M.J. A novel route to fully substituted 1H-pyrazoles. J. Org.
Chem. 2005;70:8468–8471. doi: 10.1021/jo051319a. [PubMed] [CrossRef] [Google Scholar]64. Akbas E., Berber I., Sener A., Hasanov B. Synthesis and antibacterial activity of 4-benzoyl-1-methyl-5-phenyl-1H-pyrazole-3-carboxylic acid and derivatives. Farmaco. 2005;60:23–26. doi: 10.1016/j.farmac.2004.09.003. [PubMed] [CrossRef] [Google Scholar]65. Prasath R., Bhavana P., Sarveswari S., Ng S.W., Tiekink E.R.T. Efficient ultrasound-assisted synthesis, spectroscopic, crystallographic and biological investigations of pyrazole-appended quinolinyl chalcones. J. Mol. Struct.
2015;1081:201–210. doi: 10.1016/j.molstruc.2014.10.026. [CrossRef] [Google Scholar]66. Mert S., Kasimogullari R., Ica T., Colak F., Altun A., Ok S. Synthesis, structure-activity relationships, and in vitro antibacterial and antifungal activity evaluations of novel pyrazole carboxylic and dicarboxylic acid derivatives. Eur. J. Med. Chem. 2014;78:86–96. doi: 10.1016/j.ejmech.2014.03.033. [PubMed] [CrossRef] [Google Scholar]67.
Rahimizadeh M., Pordel M., Bakavoli M., Rezaeian S., Sadeghian A.
Synthesis and antibacterial activity of some new derivatives of pyrazole. World J. Microbiol. Biotechnol. 2010;26:317–321. doi: 10.1007/s11274-009-0178-0. [CrossRef] [Google Scholar]68. Chandrakantha B., Isloor A., Shetty P., Isloor S., Malladi S., Fun H. Synthesis, characterization and antimicrobial activity of novel ethyl 1-(N-substituted)-5-phenyl-1H-pyrazole-4-carboxylate derivatives. Med. Chem. Res. 2012;21:2702–2708. doi: 10.1007/s00044-011-9796-9. [CrossRef] [Google Scholar]69. Sharma P.K., Kumar S., Kumar P., Kaushik P., Kaushik D., Dhingra Y. Synthesis and biological evaluation of some pyrazolylpyrazolines as anti-inflammatory–antimicrobial agents. Eur. J. Med. Chem. 2010;45:2650–2655. doi: 10.1016/j.ejmech.2010.01.059. [PubMed] [CrossRef] [Google Scholar]70. Kendre B.V., Landge M.G., Bhusare S.R. Synthesis and biological evaluation of some novel pyrazole, isoxazole, benzoxazepine, benzothiazepine and benzodiazepine derivatives bearing an aryl sulfonate moiety as antimicrobial and anti-inflammatory agents. Arab. J. Chem. 2015 doi: 10.1016/j.arabjc.2015.01.007. [CrossRef] [Google Scholar]71.
B'Bhatt H., Sharma S. Synthesis and antimicrobial activity of pyrazole nucleus containing 2-thioxothiazolidin-4-one derivatives.
Arab. J. Chem. 2017;10:S1590–S1596. doi: 10.1016/j.arabjc.2013.05.029. [CrossRef] [Google Scholar]72. Abunada N., Hassaneen H., Kandile N., Miqdad O. Synthesis and Antimicrobial Activity of Some New Pyrazole, Fused Pyrazolo[3,4-d]-pyrimidine and Pyrazolo[4,3-e][1,2,4]-triazolo[1,5-c]pyrimidine Derivatives. Molecules. 2008;13:1501–1517. doi: 10.3390/molecules13071501. [PMC free article] [PubMed] [CrossRef] [Google Scholar]73. Padmaja A., Payani T., Reddy G.D., Padmavathi V. Synthesis, antimicrobial and antioxidant activities of substituted pyrazoles, isoxazoles, pyrimidine and thioxopyrimidine derivatives. Eur.
J. Med. Chem. 2009;44:4557–4566. doi: 10.1016/j.ejmech.2009.06.024. [PubMed] [CrossRef] [Google Scholar]74.
Ragavan R.V., Vijayakumar V., Kumari N.S. Synthesis and antimicrobial activities of novel 1,5-diaryl pyrazoles. Eur. J. Med. Chem. 2010;45:1173–1180. doi: 10.1016/j.ejmech.2009.12.042. [PubMed] [CrossRef] [Google Scholar]75. Sharma P.K., Chandak N., Kumar P., Sharma C., Aneja K.R. Synthesis and biological evaluation of some 4-functionalized-pyrazoles as antimicrobial agents. Eur. J. Med. Chem.
2011;46:1425–1432. doi: 10.1016/j.ejmech.2011.01.060. [PubMed] [CrossRef] [Google Scholar]76. Pathak R.B., Chovatia P.T., Parekh H.H. Synthesis, antitubercular and antimicrobial evaluation of 3-(4-chlorophenyl)-4-substituted pyrazole derivatives. Bioorg. Med.
Chem. Lett. 2012;22:5129–5133. doi: 10.1016/j.bmcl.2012.05.063. [PubMed] [CrossRef] [Google Scholar]77. Vijesh A.M., Isloor A.M., Telkar S., Peethambar S.K., Rai S., Isloor N. Synthesis, characterization and antimicrobial studies of some new pyrazole incorporated imidazole derivatives. Eur. J.
Med. Chem.
2011;46:3531–3536. doi: 10.1016/j.ejmech.2011.05.005. [PubMed] [CrossRef] [Google Scholar]78. Wu J., Shi Q., Chen Z., He M., Jin L., Hu D. Synthesis and Bioactivity of Pyrazole Acyl Thiourea Derivatives.
Molecules.
2012;17:5139–5150. doi: 10.3390/molecules17055139. [PMC free article] [PubMed] [CrossRef] [Google Scholar]79. Wu Z., Hu D., Kuangn J., Cain H., Wun S., Xuen W. Synthesis and Antifungal Activity of N-(Substituted pyridinyl)-1-methyl(phenyl)-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide Derivatives. Molecules. 2012;17:14205–14218. doi: 10.3390/molecules171214205. [PMC free article] [PubMed] [CrossRef] [Google Scholar]80. Xu L.-L., Zheng C.-J., Sun L.-P., Miao J., Piao H.-R. Synthesis of novel 1,3-diaryl pyrazole derivatives bearing rhodanine-3-fatty acid moieties as potential antibacterial agents. Eur. J. Med. Chem. 2012;48:174–178.
doi: 10.1016/j.ejmech.2011.12.011. [PubMed] [CrossRef] [Google Scholar]81. Desai N.C., Rajpara K.M., Joshi V.V. Synthesis of pyrazole encompassing 2-pyridone derivatives as antibacterial agents. Bioorg. Med. Chem. Lett. 2013;23:2714–2717. doi: 10.1016/j.bmcl.2013.02.077.
[PubMed] [CrossRef] [Google Scholar]82. Jardosh H.H., Sangani C.B., Patel M.P., Patel R.G. One step synthesis of pyrido [1,2-a] benzimidazole derivatives of aryloxypyrazole and their antimicrobial evaluation. Chin. Chem. Lett. 2013;24:123–126. doi: 10.1016/j.cclet.2013.01.021. [CrossRef] [Google Scholar]83. Malladi S., Isloor A.M., Isloor S., Akhila D., Fun H.-K. Synthesis, characterization and antibacterial activity of some new pyrazole based Schiff bases. Arab. J. Chem. 2013;6:335–340. doi: 10.1016/j.arabjc.2011.10.009. [CrossRef] [Google Scholar]84. Renuka N., Kumar K.A. Synthesis and biological evaluation of novel formyl-pyrazoles bearing coumarin moiety as potent antimicrobial and antioxidant agents. Bioorg. Med. Chem. Lett. 2013;23:6406–6409. doi: 10.1016/j.bmcl.2013.09.053. [PubMed] [CrossRef] [Google Scholar]85. Song M.-X., Zheng C.-J., Deng X.-Q., Sun L.-P., Wu Y., Hong L., Li Y.J., Liu Y., Wei Z.Y., Jin M.J., et al. Synthesis and antibacterial evaluation of rhodanine-based 5-aryloxy pyrazoles against selected methicillin resistant and quinolone-resistant Staphylococcus aureus (MRSA and QRSA) Eur. J. Med. Chem.
2013;60:376–385. doi: 10.1016/j.ejmech.2012.12.007. [PubMed] [CrossRef] [Google Scholar]86. Sayed G.H., Azab M.E., Anwer K.E., Raouf M.A., Negm N.A. Pyrazole, pyrazolone and enaminonitrile pyrazole derivatives: Synthesis, characterization and potential in corrosion inhibition and antimicrobial applications. J. Mol. Liq. 2018;252:329–338. doi: 10.1016/j.molliq.2017.12.156. [CrossRef] [Google Scholar]87. Kalaria P.N., Satasia S.P., Avalani J.R., Raval D.K. Ultrasound-assisted one-pot four-component synthesis of novel 2-amino-3-cyanopyridine derivatives bearing 5-imidazopyrazole scaffold and their biological broadcast. Eur. J. Med. Chem.
2014;83:655–664. doi: 10.1016/j.ejmech.2014.06.071. [PubMed] [CrossRef] [Google Scholar]88. Kumar R., Arora J., Ruhil S., Phougat N., Chhillar A.K., Prasad A.K. Synthesis and antimicrobial studies of pyrimidine pyrazole heterocycles. Adv. Chem. 2014;2014:1–12. doi: 10.1155/2014/329681. [CrossRef] [Google Scholar]89. Liu X.-R., Wu H., He Z.-Y., Ma Z.-Q., Feng J.-T., Zhang X. Design, Synthesis and Fungicidal Activities of Some Novel Pyrazole Derivatives. Molecules. 2014;19:14036–14051. doi: 10.3390/molecules190914036. [PMC free article] [PubMed] [CrossRef] [Google Scholar]90.
Malladi S., Isloor A.M., Peethambar S., Fun H.K. Synthesis and biological evaluation of newer analogues of 2,5-disubstituted 1,3,4-oxadiazole containing pyrazole moiety as antimicrobial agents. Arab.
J. Chem. 2014;7:1185–1191. doi: 10.1016/j.arabjc.2013.12.020. [CrossRef] [Google Scholar]91. Mehta H.B., Dixit B.C., Dixit R.B. L-Proline catalyzed one-pot multi-component synthesis of 2-(1,3-diphenyl-1H-pyrazol-4-yl)quinazolin-4(3H)-one derivatives and their biological studies. Chin. Chem. Lett. 2014;25:741–744. doi: 10.1016/j.cclet.2014.03.015.
[CrossRef] [Google Scholar]92. Ningaiah S., Bhadraiah U.K., Doddaramappa S.D., Keshavamurthy S., Javarasetty C.
Novel pyrazole integrated 1,3,4-oxadiazoles: Synthesis, characterization and antimicrobial evaluation. Bioorg. Med. Chem. Lett. 2014;24:245–248. doi: 10.1016/j.bmcl.2013.11.029. [PubMed] [CrossRef] [Google Scholar]93. Prakash T.B., Reddy G.D., Padmaja A., Padmavathi V. Synthesis and antimicrobial activity of amine linked bis-and tris-heterocycles.
Eur. J. Med.
Chem. 2014;82:347–3454. doi: 10.1016/j.ejmech.2014.06.001. [PubMed] [CrossRef] [Google Scholar]94. Du S., Tian Z., Yang D., Li X., Li H., Jia C., Che C., Wang M., Qin Z. Synthesis, Antifungal Activity and Structure-Activity Relationships of Novel 3-(Difluoromethyl)-1-methyl-1H-pyrazole-4-carboxylic Acid Amides. Molecules. 2015;20:8395–8408. doi: 10.3390/molecules20058395.
[PMC free article] [PubMed] [CrossRef] [Google Scholar]95. Miniyar P.B., Barmade M.A., Mahajan A.A. Synthesis and biological evaluation of 1-(5-(2-chloroquinolin-3-yl)-3-phenyl-1H-pyrazol-1-yl) ethanone derivatives as potential antimicrobial agents.
J. Saudi Chem. Soc. 2015;19:655–660. doi: 10.1016/j.jscs.2013.12.004.
[CrossRef] [Google Scholar]96. Radi S., Tighadouini S., Feron O., Riant O., Bouakka M., Benabbes R., Mabkhot Y.N. Synthesis of Novel β-Keto-Enol Derivatives Tethered Pyrazole, Pyridine and Furan as New Potential Antifungal and Anti-Breast Cancer Agents. Molecules. 2015;20:19684–19694. doi: 10.3390/molecules201119684. [PMC free article] [PubMed] [CrossRef] [Google Scholar]97. Rizk H.F., Ibrahim S.A., El-Borai M.A. Synthesis, fastness properties, color assessment and antimicrobial activity of some azo reactive dyes having pyrazole moiety. Dyes Pigment. 2015;112:86–92. doi: 10.1016/j.dyepig.2014.06.026. [CrossRef] [Google Scholar]98. Sun J., Zhou Y. Synthesis and Antifungal Activity of the Derivatives of Novel Pyrazole Carboxamide and Isoxazolol Pyrazole Carboxylate. Molecules. 2015;20:4383–4394. doi: 10.3390/molecules20034383. [PMC free article] [PubMed] [CrossRef] [Google Scholar]99. Yu L.-G., Ni T.-F., Gao W., He Y., Wang Y.-Y., Cui H.-W., Yang C.-G., Qiu W.-W. The synthesis and antibacterial activity of pyrazole-fused tricyclic diterpene derivatives. Eur. J. Med. Chem.
2015;90:10–20. doi: 10.1016/j.ejmech.2014.11.015. [PubMed] [CrossRef] [Google Scholar]100. Elshaier Y., Barakat A., Al-Qahtany B., Al-Majid A., Al-Agamy M. Synthesis of Pyrazole-Thiobarbituric Acid Derivatives: Antimicrobial Activity and Docking Studies. Molecules. 2016;21:1337. doi: 10.3390/molecules21101337. [PMC free article] [PubMed] [CrossRef] [Google Scholar]101. Hafez H., El-Gazzar A.-R. Synthesis and Biological Evaluation of N-Pyrazolyl Derivatives and Pyrazolopyrimidine Bearing a Biologically Active Sulfonamide Moiety as Potential Antimicrobial Agent. Molecules. 2016;21:1156. doi: 10.3390/molecules21091156. [PMC free article] [PubMed] [CrossRef] [Google Scholar]102. Mabkhot Y., Alatibi F., El-Sayed N., Kheder N., Al-Showiman S. Synthesis and Structure-Activity Relationship of Some New Thiophene-Based Heterocycles as Potential Antimicrobial Agents. Molecules. 2016;21:1036. doi: 10.3390/molecules21081036. [PMC free article] [PubMed] [CrossRef] [Google Scholar]103. Mu J.-X., Shi Y.-X., Yang M.-Y., Sun Z.-H., Liu X.-H., Li B.-J., Sun N.-B. Design, Synthesis, DFT Study and Antifungal Activity of Pyrazolecarboxamide Derivatives.
Molecules. 2016;21:68. doi: 10.3390/molecules21010068. [PMC free article] [PubMed] [CrossRef] [Google Scholar]104. Nagamallu R., Srinivasan B., Ningappa M.B., Kariyappa A.K. Synthesis of novel coumarin appended bis(formylpyrazole) derivatives: Studies on their antimicrobial and antioxidant activities. Bioorg. Med. Chem. Lett. 2016;26:690–694. doi: 10.1016/j.bmcl.2015.11.038. [PubMed] [CrossRef] [Google Scholar]105. Abrigach F., Bouchal B., Riant O., Macé Y., Takfaoui A., Radi S., Oussaid A., Bellaoui M., Touzani R. New N,N,N′,N′-tetradentate Pyrazoly Agents: Synthesis and Evaluation of their Antifungal and Antibacterial Activities. Med. Chem. 2016;12:83–89.
doi: 10.2174/1573406411666150519111800. [PubMed] [CrossRef] [Google Scholar]106. El Shehry M.F., Ghorab M.M., Abbas S.Y., Fayed E.A., Shedid S.A., Ammar Y.A. Quinoline derivatives bearing pyrazole moiety: Synthesis and biological evaluation as possible antibacterial and antifungal agents. Eur. J. Med.
Chem. 2018;143:1463–1473. doi: 10.1016/j.ejmech.2017.10.046. [PubMed] [CrossRef] [Google Scholar]107. Ahn M., Gunasekaran P., Rajasekaran G., Kim E.Y., Lee S.-J., Bang G., Cho K., Hyun J.-K., Lee H.-J., Jeon Y.H., et al. Pyrazole derived ultra-short antimicrobial peptidomimetics with potent anti-biofilm activity. Eur. J. Med. Chem. 2017;125:551–564. doi: 10.1016/j.ejmech.2016.09.071. [PubMed] [CrossRef] [Google Scholar]108. Nada A., Al-Moghazy M., Soliman A.A.F., Rashwan G.M.T., Eldawy T.H.A., Hassan A.A.E., Sayed G.H. Pyrazole-based compounds in chitosan liposomal emulsion for antimicrobial cotton fabrics. Int.
J. Biol. Macromol. 2018;107:585–594. doi: 10.1016/j.ijbiomac.2017.09.031. [PubMed] [CrossRef] [Google Scholar]109. Sharma A., Ghabbour H., Khan S.T., de la Torre B.G., Albericio F., El-Faham A. Novel pyrazolyl-s-triazine derivatives, molecular structure and antimicrobial activity. J. Mol. Struct.
2017;1145:244–253. doi: 10.1016/j.molstruc.2017.05.040. [CrossRef] [Google Scholar]110. Zhou L., Wang P.-Y., Zhou J., Shao W.-B., Fang H.-S., Wu Z.-B., Yang S. Antimicrobial activities of pyridinium-tailored pyrazoles bearing 1,3,4-oxadiazole scaffolds. J. Saudi Chem. Soc. 2017;21:852–860. doi: 10.1016/j.jscs.2017.04.005.
[CrossRef] [Google Scholar]111. Mandal S., Mondal M., Biswas J.K., Cordes D.B., Slawin A.M.Z., Butcher R.J., Saha M., Saha N.C. Synthesis, characterization and antimicrobial activity of some nickel, cadmium and mercury complexes of 5-methyl pyrazole-3yl-N-(2′-methylthiophenyl) methyleneimine, (MPzOATA) ligand. J. Mol. Struct. 2018;1152:189–198. doi: 10.1016/j.molstruc.2017.09.015. [CrossRef] [Google Scholar]112. Mor S., Mohil R., Kumar D., Ahuja M. Synthesis and antimicrobial activities of some isoxazolyl thiazolyl pyrazoles.
Med.
Chem.
Res. 2012;21:3541–3548. doi: 10.1007/s00044-011-9859-y. [CrossRef] [Google Scholar]113. Nitulescu G.M., Draghici C., Chifiriuc M.C., Marutescu L., Bleotu C., Missir A.V. Synthesis and antimicrobial screening of N-(1-methyl-1H-pyrazole-4-carbonyl)-thiourea derivatives. Med. Chem. Res.
2012;21:308–314. doi: 10.1007/s00044-010-9541-9. [CrossRef] [Google Scholar]114. Tanitame A., Oyamada Y., Ofuji K., Fujimoto M., Iwai N., Hiyama Y., Suzuki K., Ito H., Terauchi H., Kawasaki M., et al. Synthesis and Antibacterial Activity of a Novel Series of Potent DNA Gyrase Inhibitors. Pyrazole Derivatives.
J. Med. Chem. 2004;47:3693–3696. doi: 10.1021/jm030394f. [PubMed] [CrossRef] [Google Scholar]115. Çetin A., Bildirici İ. A study on synthesis and antimicrobial activity of 4-acyl-pyrazoles. J. Saudi Chem. Sci. 2016 doi: 10.1016/j.jscs.2016.05.008. [CrossRef] [Google Scholar]116. Dayakar C., Kumar B.S., Sneha G., Sagarika G., Meghana K., Ramakrishna S., Prakasham R.S., China R.B. Synthesis, pharmacological activities and molecular docking studies of pyrazolyltriazoles as anti-bacterial and anti-inflammatory agents.
Bioorg. Med. Chem. 2017;25:5678–5691.
doi: 10.1016/j.bmc.2017.08.042. [PubMed] [CrossRef] [Google Scholar]117. Dai H., Chen J., Li G., Ge S., Shi Y., Fang Y., Ling Y. Design, synthesis, and bioactivities of novel oxadiazole-substituted pyrazole oximes. Bioorg. Med. Chem. Lett. 2017;27:950–953. doi: 10.1016/j.bmcl.2016.12.083. [PubMed] [CrossRef] [Google Scholar]118. Kamal A., Shaik A.B., Jain N., Kishor C., Nagabhushana A., Supriya B., Kumar G.B., Chourasiya S.S., Suresh Y., Mishra R.K. Anthony Addlagatta.
Design and synthesis of pyrazole–oxindole conjugates targeting tubulin polymerization as new anticancer agents. Eur. J. Med. Chem. 2015;92:501–513. doi: 10.1016/j.ejmech.2013.10.077. [PubMed] [CrossRef] [Google Scholar]119. Xu Y., Liu X.-H., Saunders M., Pearce S., Foulks J.M., Parnell K.M., Clifford A., Nix R.N., Bullough J., Hendrickson T.F., et al. Discovery of 3-(trifluoromethyl)-1H-pyrazole-5-carboxamide activators of the M2 isoform of pyruvate kinase (PKM2) Bioorg.
Med. Chem. Lett. 2014;24:515–519. doi: 10.1016/j.bmcl.2013.12.028. [PubMed] [CrossRef] [Google Scholar]120. Viale M., Anzaldi M., Aiello C., Fenoglio C., Albicini F., Emionite L., Gangemi R., Balbi A. Evaluation of the anti-proliferative activity of three new pyrazole compounds in sensitive and resistant tumor cell lines. Pharmacol. Rep. 2013;65:717–723. doi: 10.1016/S1734-1140(13)71050-8. [PubMed] [CrossRef] [Google Scholar]121. Tzanetou E., Liekens S., Kasiotis K.M., Fokialakis N., Haroutounian S.A. Novel Pyrazole and Indazole Derivatives: Synthesis and Evaluation of Their Anti-Proliferative and Anti-Angiogenic Activities. Arch. Pharm.
2012;345:804–811. doi: 10.1002/ardp.201200057. [PubMed] [CrossRef] [Google Scholar]122. Zheng L.-W., Shao J.-H., Zhao B.-X., Miao J.-Y. Synthesis of novel pyrazolo[1,5-a]pyrazin-4(5H)-one derivatives and their inhibition against growth of A549 and H322 lung cancer cells.
Bioorg. Med.
Chem.
Lett. 2011;21:3909–3913. doi: 10.1016/j.bmcl.2011.05.035. [PubMed] [CrossRef] [Google Scholar]123. Balbi A., Anzaldi M., Macciò C., Aiello C., Mazzei M., Gangemi R., Castagnola P., Miele M., Rosano C., Viale M. Synthesis and biological evaluation of novel pyrazole derivatives with anticancer activity. Eur. J. Med. Chem. 2011;46:5293–5309. doi: 10.1016/j.ejmech.2011.08.014.
[PubMed] [CrossRef] [Google Scholar]124. Nitulescu G.M., Draghici C., Missir A.V. Synthesis of new pyrazole derivatives and their anticancer evaluation. Eur. J. Med. Chem. 2010;45:4914–4919. doi: 10.1016/j.ejmech.2010.07.064.
[PubMed] [CrossRef] [Google Scholar]125. Bandgar B.P., Totre J.V., Gawande S.S., Khobragade C.N., Warangkar S.C., Kadam P.D. Synthesis of novel 3,5-diaryl pyrazole derivatives using combinatorial chemistry as inhibitors of tyrosinase as well as potent anticancer, anti-inflammatory agents.
Bioorg. Med. Chem. 2010;18:6149–6155. doi: 10.1016/j.bmc.2010.06.046. [PubMed] [CrossRef] [Google Scholar]126. Zheng L.-W., Wu L.-L., Zhao B.-X., Dong W.-L., Miao J.-Y. Synthesis of novel substituted pyrazole-5-carbohydrazide hydrazone derivatives and discovery of a potent apoptosis inducer in A549 lung cancer cells. Bioorg.
Med. Chem. 2009;17:1957–1962. doi: 10.1016/j.bmc.2009.01.037. [PubMed] [CrossRef] [Google Scholar]127. Xia Y., Dong Z.-W., Zhao B.-X., Ge X., Meng N., Shin D.-S., Miao J.-Y. Synthesis and structure-activity relationships of novel 1-arylmethyl-3-aryl-1H-pyrazole-5-carbohydrazide derivatives as potential agents against A549 lung cancer cells. Bioorg.
Med. Chem. 2007;15:6893–6899. doi: 10.1016/j.bmc.2007.08.021. [PubMed] [CrossRef] [Google Scholar]128. Lian S., Su H., Zhao B.X., Liu W.Y., Zheng L.W., Miao J.Y. Synthesis and discovery of pyrazole-5-carbohydrazide N-glycosides as inducer of autophagy in A549 lung cancer cells. Bioorg. Med. Chem. 2009;17:7085–7092.
doi: 10.1016/j.bmc.2009.09.004. [PubMed] [CrossRef] [Google Scholar]129. Wei F., Zhao B.-X., Huang B., Zhang L., Sun C.-H., Dong W.-L., Shin D.-S., Miao J.-Y.
Design, synthesis, and preliminary biological evaluation of novel ethyl 1-(2′-hydroxy-3′-aroxypropyl)-3-aryl-1H-pyrazole-5-carboxylate. Bioorg. Med. Chem. Lett. 2006;16:6342–6347. doi: 10.1016/j.bmcl.2006.09.008. [PubMed] [CrossRef] [Google Scholar]130.
Ding X.-L., Zhang H.-Y., Qi L., Zhao B.-X., Lian S., Lv H.-S., Miao J.-Y. Synthesis of novel pyrazole carboxamide derivatives and discovery of modulators for apoptosis or autophagy in A549 lung cancer cells.
Bioorg. Med.
Chem. Lett. 2009;19:5325–5328.
doi: 10.1016/j.bmcl.2009.07.131. [PubMed] [CrossRef] [Google Scholar]131. Zheng L.-W., Li Y., Ge D., Zhao B.-X., Liu Y.-R., Lv H.-S., Ding J., Miao J.-Y. Synthesis of novel oxime-containing pyrazole derivatives and discovery of regulators for apoptosis and autophagy in A549 lung cancer cells. Bioorg. Med. Chem. Lett. 2010;20:4766–4770.
doi: 10.1016/j.bmcl.2010.06.121. [PubMed] [CrossRef] [Google Scholar]132. Liu Y.-R., Luo J.-Z., Duan P.-P., Shaon J., Zhao B.-X., Miao J.-Y. Synthesis of pyrazole peptidomimetics and their inhibition against A549 lung cancer cells. Bioorg. Med.
Chem. Lett. 2012;22:6882–6887. doi: 10.1016/j.bmcl.2012.09.032. [PubMed] [CrossRef] [Google Scholar]133. Fan C.-D., Zhao B.-X., Wei F., Zhang G.-H., Dong W.-L., Miao J.-Y.
Synthesis and discovery of autophagy inducers for A549 and H460 lung cancer cells, novel 1-(2′-hydroxy-3′-aroxypropyl)-3-aryl-1H-pyrazole-5-carbohydrazide derivatives. Bioorg. Med. Chem. Lett. 2008;18:3860–3864. doi: 10.1016/j.bmcl.2008.06.058. [PubMed] [CrossRef] [Google Scholar]134. Shen S.-L., Zhu J., Li M., Zhao B.-X., Miao J.-Y. Synthesis of ferrocenyl pyrazole-containing chiral aminoethanol derivatives and their inhibition against A549 and H322 lung cancer cells. Eur. J. Med. Chem.
2012;54:287–294.
doi: 10.1016/j.ejmech.2012.05.008. [PubMed] [CrossRef] [Google Scholar]135. Farag A.M., Mayhoub A.S., Barakat S.E., Bayomi A.H. Regioselective synthesis and antitumor screening of some novel N-phenylpyrazole derivatives. Bioorg. Med. Chem. 2008;16:881–889. doi: 10.1016/j.bmc.2007.10.015. [PubMed] [CrossRef] [Google Scholar]136. Jin C.H., Krishnaiah M., Sreenu D., Subrahmanyam V.B., Rao K.S., Mohan A.V.N., Park C.-Y., Son J.-Y., Sheen Y.Y. Synthesis and biological evaluation of 1-substituted-3-(6-methylpyridin-2-yl)-4-([1,2,4] triazolo[1,5-a]pyridin-6-yl) pyrazoles as transforming growth factor-β type 1 receptor kinase inhibitors. Bioorg. Med. Chem. Lett. 2011;21:6049–6053.
doi: 10.1016/j.bmcl.2011.08.064. [PubMed] [CrossRef] [Google Scholar]137. Newhouse B.J., Hansen J.D., Grina J., Welch M., Topalov G., Littman N., Callejo M., Martinsona M., Galbraitha S., Laird E.R., et al. Non-oxime pyrazole based inhibitors of B-Raf kinase. Bioorg. Med. Chem. Lett. 2011;21:3488–3492. doi: 10.1016/j.bmcl.2010.12.038. [PubMed] [CrossRef] [Google Scholar]138. Zhang D., Wang G., Zhao G., Xu W., Huo L. Synthesis and cytotoxic activity of novel 3-(1H-indol-3-yl)-1H-pyrazole-5-carbohydrazide derivatives. Eur. J. Med. Chem. 2011;46:5868–5877. doi: 10.1016/j.ejmech.2011.09.049. [PubMed] [CrossRef] [Google Scholar]139. Baciu-Atudosie L., Ghinet A., Farce A., Dubois J., Belei D., Bîcu E.
Synthesis and biological evaluation of new phenothiazine derivatives bearing a pyrazole unit as protein farnesyltransferase inhibitors.
Bioorg. Med.
Chem. Lett. 2012;22:6896–6902. doi: 10.1016/j.bmcl.2012.09.030. [PubMed] [CrossRef] [Google Scholar]140. Bai X.-G., Yu D.-K., Wang J.-X., Zhang H., He H.-W., Shao R.-G., Li X.-M., Wang Y.-C. Design, synthesis and anticancer activity of 1-acyl-3-amino-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole derivatives. Bioorg. Med. Chem. Lett. 2012;22:6947–6951. doi: 10.1016/j.bmcl.2012.08.117. [PubMed] [CrossRef] [Google Scholar]141. Bavetsias V., Crumpler S., Sun C., Avery S., Atrash B., Faisal A., Moore A.S., Kosmopoulou M., Brown N., Sheldrake P.W., et al.
Optimization of imidazo[4,5-b]pyridine-based kinase inhibitors: Identification of a dual FLT3/Aurora kinase inhibitor as an orally bioavailable preclinical development candidate for the treatment of acute myeloid leukemia. J. Med. Chem. 2012;55:8721–8734. doi: 10.1021/jm300952s. [PMC free article] [PubMed] [CrossRef] [Google Scholar]142. Bondock S., Adel S., Etman H.A., Badria F.A. Synthesis and antitumor evaluation of some new 1,3,4-oxadiazole-based heterocycles. Eur. J. Med. Chem. 2012;48:192–199. doi: 10.1016/j.ejmech.2011.12.013. [PubMed] [CrossRef] [Google Scholar]143. Cui J.J., McTigue M., Nambu M., Tran-Dubé M., Pairish M., Shen H., Jia L., Cheng H., Hoffman J., Le P., et al. Discovery of a Novel Class of Exquisitely Selective Mesenchymal-Epithelial Transition Factor (c-MET) Protein Kinase Inhibitors and Identification of the Clinical Candidate 2-(4-(1-(Quinolin-6-ylmethyl)-1H-[1,2,3]triazolo[4,5-b]pyrazin-6-yl)-1H-pyrazol-1-yl)ethanol (PF-04217903) for the Treatment of Cancer. J. Med. Chem. 2012;55:8091–8109. doi: 10.1021/jm300967g. [PubMed] [CrossRef] [Google Scholar]144. El Hamid M.K.A., Mihovilovic M.D., El-Nassan H.B. Synthesis of novel pyrazolo[3,4-d]pyrimidine derivatives as potential anti-breast cancer agents. Eur. J.
Med.
Chem. 2012;57:323–328. doi: 10.1016/j.ejmech.2012.09.031. [PubMed] [CrossRef] [Google Scholar]145. El-Borai M., Rizk H., Abd-Aal M., El-Deeb I. Synthesis of pyrazolo[3,4-b]pyridines under microwave irradiation in multi-component reactions and their antitumor and antimicrobial activities–Part 1. Eur. J. Med. Chem. 2012;48:92–96. doi: 10.1016/j.ejmech.2011.11.038. [PubMed] [CrossRef] [Google Scholar]146. Hanan E.J., Van Abbema A., Barrett K., Blair W.S., Blaney J., Chang C., Eigenbrot C., Flynn S., Gibbons P., Hurley C.A., et al. Discovery of potent and selective pyrazolopyrimidine janus kinase 2 inhibitors. J. Med. Chem.
2012;55:10090–100107. doi: 10.1021/jm3012239. [PubMed] [CrossRef] [Google Scholar]147. Huang Y.-Y., Wang L.-Y., Chang C.-H., Kuo Y.-H., Kaneko K., Takayama H., Kimura M., Juang S.-H., Wong F.F. One-pot synthesis and antiproliferative evaluation of pyrazolo[3,4-d]pyrimidine derivatives. Tetrahedron. 2012;68:9658–9664. doi: 10.1016/j.tet.2012.09.054. [CrossRef] [Google Scholar]148. Li X., Lu X., Xing M., Yang X.-H., Zhao T.-T., Gong H.-B., Zhu H.-L.
Synthesis, biological evaluation, and molecular docking studies of N,1,3-triphenyl-1H-pyrazole-4-carboxamide derivatives as anticancer agents. Bioorg. Med. Chem. Lett. 2012;22:3589–3593. doi: 10.1016/j.bmcl.2012.04.066. [PubMed] [CrossRef] [Google Scholar]149. Metwally M., Gouda M., Harmal A.N., Khalil A. Synthesis, antitumor, cytotoxic and antioxidant evaluation of some new pyrazolotriazines attached to antipyrine moiety. Eur. J. Med. Chem. 2012;56:254–262. doi: 10.1016/j.ejmech.2012.08.034. [PubMed] [CrossRef] [Google Scholar]150. Mohareb R.M., Al-Omran F. Reaction of pregnenolone with cyanoacetylhydrazine: Novel synthesis of hydrazide–hydrazone, pyrazole, pyridine, thiazole, thiophene derivatives and their cytotoxicity evaluations. Steroids.
2012;77:1551–1559. doi: 10.1016/j.steroids.2012.09.007. [PubMed] [CrossRef] [Google Scholar]151. Mohareb R.M., Wardakhan W.W., Elmegeed G.A., Ashour R.M. Heterocyclizations of pregnenolone: Novel synthesis of thiosemicarbazone, thiophene, thiazole, thieno[2,3-b]pyridine derivatives and their cytotoxicity evaluations. Steroids. 2012;77:1560–1569. doi: 10.1016/j.steroids.2012.09.004. [PubMed] [CrossRef] [Google Scholar]152. Puthiyapurayil P., Poojary B., Chikkanna C., Buridipad S.K. Design, synthesis and biological evaluation of a novel series of 1,3,4-oxadiazole bearing N-methyl-4-(trifluoromethyl) phenyl pyrazole moiety as cytotoxic agents. Eur.
J.
Med. Chem. 2012;53:203–210. doi: 10.1016/j.ejmech.2012.03.056. [PubMed] [CrossRef] [Google Scholar]153. Strocchi E., Fornari F., Minguzzi M., Gramantieri L., Milazzo M., Rebuttini V., Breviglieri S., Camaggi C.M., Locatelli E., Bolondi L., et al. Design, synthesis and biological evaluation of pyrazole derivatives as potential multi-kinase inhibitors in hepatocellular carcinoma. Eur.
J. Med. Chem. 2012;48:391–401. doi: 10.1016/j.ejmech.2011.12.031. [PubMed] [CrossRef] [Google Scholar]154.
Vujasinović I., Paravić-Radičević A., Mlinarić-Majerski K., Brajša K., Bertoša B. Synthesis and biological validation of novel pyrazole derivatives with anticancer activity guided by 3D-QSAR analysis. Bioorg. Med. Chem. 2012;20:2101–2110. doi: 10.1016/j.bmc.2012.01.032. [PubMed] [CrossRef] [Google Scholar]155.
Yamamoto S., Tomita N., Suzuki Y., Suzaki T., Kaku T., Hara T., Yamaokaa M., Kanzakia N., Hasuokaa A., Babaa A., et al. Design, synthesis, and biological evaluation of 4-arylmethyl-1-phenylpyrazole and 4-aryloxy-1-phenylpyrazole derivatives as novel androgen receptor antagonists.
Bioorg. Med. Chem. 2012;20:2338–2352. doi: 10.1016/j.bmc.2012.02.005. [PubMed] [CrossRef] [Google Scholar]156. Al-Adiwish W.M., Tahir M., Siti-Noor-Adnalizawati A., Hashim S.F., Ibrahim N., Yaacob W. Synthesis, antibacterial activity and cytotoxicity of new fused pyrazolo[1,5-a]pyrimidine and pyrazolo[5,1-c][1,2,4]triazine derivatives from new 5-aminopyrazoles. Eur. J. Med. Chem. 2013;64:464–476. doi: 10.1016/j.ejmech.2013.04.029. [PubMed] [CrossRef] [Google Scholar]157. Bavetsias V., Faisal A., Crumpler S., Brown N., Kosmopoulou M., Joshi A., Atrash B., Pérez-Fuertes Y., Schmitt J.A., Boxall K.J., et al. Aurora isoform selectivity: Design and synthesis of imidazo[4,5-b]pyridine derivatives as highly selective inhibitors of Aurora-A kinase in cells. J. Med. Chem. 2013;56:9122–9135. doi: 10.1021/jm401115g. [PMC free article] [PubMed] [CrossRef] [Google Scholar]158.
Desai B., Dixon K., Farrant E., Feng Q., Gibson K.R., Van Hoorn W.P., Mills J., Morgan T., Parry D.M., Ramjee M.K., et al. Rapid discovery of a novel series of Abl kinase inhibitors by application of an integrated microfluidic synthesis and screening platform. J. Med. Chem. 2013;56:3033–3047. doi: 10.1021/jm400099d.
[PubMed] [CrossRef] [Google Scholar]159.
Kamal A., Tamboli J.R., Vishnuvardhan M., Adil S., Nayak V.L., Ramakrishna S. Synthesis and anticancer activity of heteroaromatic linked 4β-amido podophyllotoxins as apoptotic inducing agents. Bioorg. Med. Chem. Lett. 2013;23:273–280. doi: 10.1016/j.bmcl.2012.10.099. [PubMed] [CrossRef] [Google Scholar]160. Koca I., Özgür A., Coşkun K.A., Tutar Y.
Synthesis and anticancer activity of acyl thioureas bearing pyrazole moiety. Bioorg. Med. Chem. 2013;21:3859–3865.
doi: 10.1016/j.bmc.2013.04.021. [PubMed] [CrossRef] [Google Scholar]161. Miyamoto N., Sakai N., Hirayama T., Miwa K., Oguro Y., Oki H., Okada K., Takagi T., Iwata H., Awazu Y., et al. Discovery of N-[5-({2-[(cyclopropylcarbonyl) amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (TAK-593), a highly potent VEGFR2 kinase inhibitor. Bioorg. Med. Chem. 2013;21:2333–2345. doi: 10.1016/j.bmc.2013.01.074. [PubMed] [CrossRef] [Google Scholar]162.
Shen S.-L., Shao J.-H., Luo J.-Z., Liu J.-T., Miao J.-Y., Zhao B.-X. Novel chiral ferrocenylpyrazolo[1,5-a][1,4]diazepin-4-one derivatives–synthesis, characterization and inhibition against lung cancer cells. Eur. J. Med. Chem. 2013;63:256–268. doi: 10.1016/j.ejmech.2013.02.016. [PubMed] [CrossRef] [Google Scholar]163. Zhu S.-L., Wu Y., Liu C.-J., Wei C.-Y., Tao J.-C., Liu H.-M. Synthesis and in vitro cytotoxic activity evaluation of novel heterocycle bridged carbothioamide type isosteviol derivatives as antitumor agents. Bioorg. Med. Chem. Lett. 2013;23:1343–1346. doi: 10.1016/j.bmcl.2012.12.091. [PubMed] [CrossRef] [Google Scholar]164. Zhu S.-L., Wu Y., Liu C.-J., Wei C.-Y., Tao J.-C., Liu H.-M. Design and stereoselective synthesis of novel isosteviol-fused pyrazolines and pyrazoles as potential anticancer agents. Eur. J. Med. Chem. 2013;65:70–82. doi: 10.1016/j.ejmech.2013.04.044. [PubMed] [CrossRef] [Google Scholar]165.
Ali A.R., El-Bendary E.R., Ghaly M.A., Shehata I.A. Synthesis, in vitro anticancer evaluation and in silico studies of novel imidazo[2,1-b]thiazole derivatives bearing pyrazole moieties. Eur. J. Med. Chem. 2014;75:492–500. doi: 10.1016/j.ejmech.2013.12.010.
[PubMed] [CrossRef] [Google Scholar]166.
Sun J., Lv X.-H., Qiu H.-Y., Wang Y.-T., Du Q.-R., Li D.-D., Yang Y.-H., Zhu H.-L. Synthesis, biological evaluation and molecular docking studies of pyrazole derivatives coupling with a thiourea moiety as novel CDKs inhibitors. Eur. J. Med. Chem. 2013;68:1–9. doi: 10.1016/j.ejmech.2013.07.003. [PubMed] [CrossRef] [Google Scholar]167. Zheng Y., Zheng M., Ling X., Liu Y., Xue Y., An L., Gu N., Jin M. Design, synthesis, quantum chemical studies and biological activity evaluation of pyrazole–benzimidazole derivatives as potent Aurora A/B kinase inhibitors. Bioorg. Med. Chem. Lett. 2013;23:3523–3530. doi: 10.1016/j.bmcl.2013.04.039. [PubMed] [CrossRef] [Google Scholar]168. Cankara P.Ş., Çalışkan B., Durmaz I., Atalay R., Banoglu E. Synthesis and preliminary mechanistic evaluation of 5-(p-tolyl)-1-(quinolin-2-yl)pyrazole-3-carboxylic acid amides with potent antiproliferative activity on human cancer cell lines. Eur. J. Med. Chem. 2014;87:140–149. doi: 10.1016/j.ejmech.2014.09.056.
[PubMed] [CrossRef] [Google Scholar]169. Hopa C., Yildirim H., Kara H., Kurtaran R., Alkan M. Synthesis, characterization and anti-proliferative activity of Cd (II) complexes with NNN type pyrazole-based ligand and pseudohalide ligands as coligand. Spectrochim. Acta A Mol. Biomol. Spectrosc. 2014;121:282–287. doi: 10.1016/j.saa.2013.10.028.
[PubMed] [CrossRef] [Google Scholar]170. Jin C.H., Krishnaiah M., Sreenu D., Subrahmanyam V.B., Park H.-J., Park S.-J., Sheena Y.Y., Kim D.-K. 4-([1,2,4]Triazolo[1,5-a]pyridin-6-yl)-5(3)-(6-methylpyridin-2-yl) imidazole and-pyrazole derivatives as potent and selective inhibitors of transforming growth factor-β type I receptor kinase. Bioorg. Med. Chem. 2014;22:2724–2732. doi: 10.1016/j.bmc.2014.03.022. [PubMed] [CrossRef] [Google Scholar]171. Li S., Xu S., Tang Y., Ding S., Zhang J., Wang S., Zhou G., Zhou C., Li X. Synthesis, anticancer activity and DNA-binding properties of novel 4-pyrazolyl-1,8-naphthalimide derivatives. Bioorg. Med. Chem. Lett. 2014;24:586–590.
doi: 10.1016/j.bmcl.2013.12.014. [PubMed] [CrossRef] [Google Scholar]172. Park B.S., Al-Sanea M.M., Abdelazem A.Z., Park H.M., Roh E.J., Park H.-M., Yoo K.H., Sim T., Tae J.S., Lee S.H. Structure-based optimization and biological evaluation of trisubstituted pyrazole as a core structure of potent ROS1 kinase inhibitors. Bioorg. Med. Chem. 2014;22:3871–3878. doi: 10.1016/j.bmc.2014.06.020. [PubMed] [CrossRef] [Google Scholar]173. Reddy G.L., Guru S.K., Srinivas M., Pathania A.S., Mahajan P., Nargotra A., Bhushan S., Vishwakarma R.A., Sawantad S.D. Synthesis of 5-substituted-1H-pyrazolo[4,3-d]pyrimidin-7(6H)-one analogs and their biological evaluation as anticancer agents: MTOR inhibitors. Eur. J. Med. Chem. 2014;80:201–208. doi: 10.1016/j.ejmech.2014.04.051. [PubMed] [CrossRef] [Google Scholar]174. Wang S.-F., Zhu Y.-L., Zhu P.-T., Makawana J.A., Zhang Y.-L., Zhao M.-Y., Lv P.-C., Zhu H.-L. Design, synthesis and biological evaluation of novel 5-phenyl-1H-pyrazole derivatives as potential BRAF V600E inhibitors. Bioorg. Med. Chem. 2014;22:6201–6208. doi: 10.1016/j.bmc.2014.08.029.
[PubMed] [CrossRef] [Google Scholar]175.
Yao Y., Liao C., Li Z., Wang Z., Sun Q., Liu C., Yang Y., Tu Z., Jiang S. Design, synthesis, and biological evaluation of 1,3-disubstituted-pyrazole derivatives as new class I and IIb histone deacetylase inhibitors. Eur.
J. Med. Chem. 2014;86:639–652. doi: 10.1016/j.ejmech.2014.09.024. [PubMed] [CrossRef] [Google Scholar]176. Zhang J.-F., Li M., Miao J.-Y., Zhao B.-X. Biological activities of novel pyrazolyl hydroxamic acid derivatives against human lung cancer cell line A549. Eur. J. Med. Chem. 2014;83:516–525. doi: 10.1016/j.ejmech.2014.06.065. [PubMed] [CrossRef] [Google Scholar]177. Abd El-Karim S.S., Anwar M.M., Mohamed N.A., Nasr T., Elseginy S.A. Design, synthesis, biological evaluation and molecular docking studies of novel benzofuran–pyrazole derivatives as anticancer agents. Bioorg. Chem. 2015;63:1–12. doi: 10.1016/j.bioorg.2015.08.006. [PubMed] [CrossRef] [Google Scholar]178. Aware V., Gaikwad N., Chavan S., Manohar S., Bose J., Khanna S., B-Rao C., Dixit N., Singhd K.S., Damred A., et al.
Cyclopentyl-pyrimidine based analogues as novel and potent IGF-1R inhibitor. Eur. J. Med. Chem. 2015;92:246–256.
doi: 10.1016/j.ejmech.2014.12.053. [PubMed] [CrossRef] [Google Scholar]179. Ibrahim H.S., Abou-Seri S.M., Tanc M., Elaasser M.M., Abdel-Aziz H.A., Supuran C.T. Isatin-pyrazole benzenesulfonamide hybrids potently inhibit tumor-associated carbonic anhydrase isoforms IX and XII. Eur. J. Med. Chem. 2015;103:583–593.
doi: 10.1016/j.ejmech.2015.09.021. [PubMed] [CrossRef] [Google Scholar]180. Kamal A., Shaik A.B., Polepalli S., Kumar G.B., Reddy V.S., Mahesh R., Garimella S., Jain N. Synthesis of arylpyrazole linked benzimidazole conjugates as potential microtubule disruptors. Bioorg. Med. Chem. 2015;23:1082–1095. doi: 10.1016/j.bmc.2015.01.004. [PubMed] [CrossRef] [Google Scholar]181. Khloya P., Ceruso M., Ram S., Supuran C.T., Sharma P.K. Sulfonamide bearing pyrazolylpyrazolines as potent inhibitors of carbonic anhydrase isoforms I, II, IX and XII. Bioorg.
Med.
Chem. Lett. 2015;25:3208–3212. doi: 10.1016/j.bmcl.2015.05.096. [PubMed] [CrossRef] [Google Scholar]182.
Maggio B., Raimondi M.V., Raffa D., Plescia F., Cascioferro S., Cancemi G., Tolomeo M., Grimaudo S., Daidone G. Synthesis and antiproliferative activity of 3-(2-chloroethyl)-5-methyl-6-phenyl-8-(trifluoromethyl)-5,6-dihydropyrazolo[3,4-f][1,2,3,5]tetrazepin-4-(3H)-one. Eur. J. Med. Chem. 2015;96:98–104. doi: 10.1016/j.ejmech.2015.04.004. [PubMed] [CrossRef] [Google Scholar]183. Nitulescu G.M., Draghici C., Olaru O.T., Matei L., Ioana A., Dragu L.D., Bleotu C. Synthesis and apoptotic activity of new pyrazole derivatives in cancer cell lines. Bioorg. Med. Chem. 2015;23:5799–5808. doi: 10.1016/j.bmc.2015.07.010. [PubMed] [CrossRef] [Google Scholar]184. Nitulescu G.M., Matei L., Aldea I.M., Draghici C., Olaru O.T., Bleotu C. Ultrasound-assisted synthesis and anticancer evaluation of new pyrazole derivatives as cell cycle inhibitors. Arab. J. Chem. 2015 doi: 10.1016/j.arabjc.2015.12.006. [CrossRef] [Google Scholar]185. Rai U.S., Isloor A.M., Shetty P., Pai K., Fun H.-K. Synthesis and in vitro biological evaluation of new pyrazole chalcones and heterocyclic diamides as potential anticancer agents. Arab. J. Chem. 2015;8:317–321. doi: 10.1016/j.arabjc.2014.01.018. [CrossRef] [Google Scholar]186. Reddy T.S., Kulhari H., Reddy V.G., Bansal V., Kamal A., Shukla R. Design, synthesis and biological evaluation of 1,3-diphenyl-1H-pyrazole derivatives containing benzimidazole skeleton as potential anticancer and apoptosis inducing agents.
Eur. J. Med. Chem. 2015;101:790–805. doi: 10.1016/j.ejmech.2015.07.031. [PubMed] [CrossRef] [Google Scholar]187.
Siddiqui T., Alam M.G., Dar A.M. Synthesis, characterization and anticancer studies of new steroidal oxadiazole, pyrrole and pyrazole derivatives. J. Saudi Chem.
Soc. 2015;19:387–391. doi: 10.1016/j.jscs.2012.04.009.
[CrossRef] [Google Scholar]188. Shi J.B., Tang W.J., Li R., Liu X.H. Novel pyrazole-5-carboxamide and pyrazole–pyrimidine derivatives: Synthesis and anticancer activity. Eur. J. Med. Chem. 2015;90:889–896.
doi: 10.1016/j.ejmech.2014.12.013. [PubMed] [CrossRef] [Google Scholar]189. Alam R., Wahi D., Singh R., Sinha D., Tandon V., Grover A. Design, synthesis, cytotoxicity, HuTopoIIα inhibitory activity and molecular docking studies of pyrazole derivatives as potential anticancer agents. Bioorg. Chem. 2016;69:77–90. doi: 10.1016/j.bioorg.2016.10.001.
[PubMed] [CrossRef] [Google Scholar]190. Lv X.-H., Ren Z.-L., Zhou B.-G., Li Q.-S., Chu M.-J., Liu D.-H., Zhang L.-S., Yao X.-K., Cao H.-Q. Discovery of N-(benzyloxy)-1,3-diphenyl-1H-pyrazole-4-carboxamide derivatives as potential antiproliferative agents by inhibiting MEK. Bioorg. Med. Chem. 2016;24:4652–4659. doi: 10.1016/j.bmc.2016.08.002.
[PubMed] [CrossRef] [Google Scholar]191. Wang F.-Q., Yang H., He B., Jia Y.-K., Meng S.-Y., Zhang C., Liu H.-M., Liu F.-W. A novel domino approach for synthesis of indolyl tetrahydropyrano[4,3-c]pyrazole derivatives as anticancer agents. Tetrahedron. 2016;72:5769–5775. doi: 10.1016/j.tet.2016.07.078. [CrossRef] [Google Scholar]192. Wen J., Bao Y., Niu Q., Yang J., Fan Y., Li J., Jing Y., Zhao L., Liu D. Identification of N-(6-mercaptohexyl)-3-(4-pyridyl)-1H-pyrazole-5-carboxamide and its disulfide prodrug as potent histone deacetylase inhibitors with in vitro and in vivo anti-tumor efficacy. Eur. J. Med. Chem. 2016;109:350–359. doi: 10.1016/j.ejmech.2016.01.013.
[PubMed] [CrossRef] [Google Scholar]193. Galal S.A., Abdelsamie A.S., Shouman S.A., Attia Y.M., Ali H.I., Tabll A., El-Shenawye R., El Abd Y.S., Ali M.M., Mahmoud A.E., et al. Part I: Design, synthesis and biological evaluation of novel pyrazole-benzimidazole conjugates as checkpoint kinase 2 (Chk2) inhibitors with studying their activities alone and in combination with genotoxic drugs. Eur. J. Med. Chem. 2017;134:392–405. doi: 10.1016/j.ejmech.2017.03.090. [PubMed] [CrossRef] [Google Scholar]194. Huang Q., Zhang S., Zhang S., Wang K., Xiao Y. Solvent and Copper Ion-Induced Synthesis of Pyridyl–Pyrazole-3-One Derivatives: Crystal Structure, Cytotoxicity. Molecules. 2017;22:1813. doi: 10.3390/molecules22111813. [PMC free article] [PubMed] [CrossRef] [Google Scholar]195. Li J., Huo H., Guo R., Liu B., Li L., Dan W., Xiao X., Zhang J., Shi B. Facile and efficient access to Androsten-17-(1′,3′,4′)-pyrazoles and Androst-17β-(1′,3′,4′)-pyrazoles via Vilsmeier reagents, and their antiproliferative activity evaluation in vitro. Eur. J. Med. Chem. 2017;130:1–14. doi: 10.1016/j.ejmech.2017.02.033. [PubMed] [CrossRef] [Google Scholar]196. Shi W., Hu J., Bao N., Li D., Chen L., Sun J. Design, synthesis and cytotoxic activities of scopoletin-isoxazole and scopoletin-pyrazole hybrids. Bioorg. Med. Chem. Lett. 2017;27:147–151. doi: 10.1016/j.bmcl.2016.11.089. [PubMed] [CrossRef] [Google Scholar]197. Wang M., Xu S., Lei H., Wang C., Xiao Z., Jia S., Zhi J., Zheng P., Zhu W. Design, synthesis and antitumor activity of Novel Sorafenib derivatives bearing pyrazole scaffold. Bioorg. Med. Chem. 2017;25:5754–5763. doi: 10.1016/j.bmc.2017.09.003. [PubMed] [CrossRef] [Google Scholar]198. Daidone G., Maggio B., Raffa D., Plescia S., Schillaci D., Raimondi M.V. Synthesis and in vitro antileukemic activity of new 4-triazenopyrazole derivatives. Farmaco. 2004;59:413–417. doi: 10.1016/j.farmac.2004.01.016.
[PubMed] [CrossRef] [Google Scholar]199.
Kamble R.D., Meshram R.J., Hese S.V., More R.A., Kamble S.S., Gacche R.N., Dawane B.S. Synthesis and in silico investigation of thiazoles bearing pyrazoles derivatives as anti-inflammatory agents. Comput. Biol. Chem. 2016;61:86–96. doi: 10.1016/j.compbiolchem.2016.01.007. [PubMed] [CrossRef] [Google Scholar]200. Bekhit A.A., Abdel-Aziem T. Design, synthesis and biological evaluation of some pyrazole derivatives as anti-inflammatory-antimicrobial agents. Bioorg. Med. Chem. 2004;12:1935–1945. doi: 10.1016/j.bmc.2004.01.037.
[PubMed] [CrossRef] [Google Scholar]201. Bekhit A.A., Ashour H.M.A., Abdel Ghany Y.S., Bekhit A.-A., Baraka A.
Synthesis and biological evaluation of some thiazolyl and thiadiazolyl derivatives of 1H-pyrazole as anti-inflammatory antimicrobial agents. Eur. J. Med. Chem. 2008;43:456–463. doi: 10.1016/j.ejmech.2007.03.030. [PubMed] [CrossRef] [Google Scholar]202. Girisha K.S., Kalluraya B., Narayana V., Padmashree V. Synthesis and pharmacological study of

1-acetyl/propyl-3-aryl-5-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-2-pyrazoline. Eur. J. Med. Chem. 2010;45:4640–4644. doi: 10.1016/j.ejmech.2010.07.032. [PubMed] [CrossRef] [Google Scholar]203. Brullo C., Spisani S., Selvatici R., Bruno O. N-Aryl-2-phenyl-2,3-dihydro-imidazo[1,2-b]pyrazole-1-carboxamides 7-substituted strongly inhibiting both fMLP-OMe-and IL-8-induced human neutrophil chemotaxis. Eur. J. Med. Chem. 2012;47:573–579. doi: 10.1016/j.ejmech.2011.11.031. [PubMed] [CrossRef] [Google Scholar]204. El-Moghazy S., Barsoum F., Abdel-Rahman H., Marzouk A. Synthesis and anti-inflammatory activity of some pyrazole derivatives. Med. Chem. Res. 2012;21:1722–1733. doi: 10.1007/s00044-011-9691-4. [CrossRef] [Google Scholar]205.
Magda A.-A., Abdel-Aziz N.I., Alaa A.-M., El-Azab A.S., ElTahir K.E. Synthesis, biological evaluation and molecular modeling study of pyrazole and pyrazoline derivatives as selective COX-2 inhibitors and anti-inflammatory agents. Part 2. Bioorg. Med.
Chem. 2012;20:3306–3316. doi: 10.1016/j.bmc.2012.03.044. [PubMed] [CrossRef] [Google Scholar]206. Qiu K.-M., Yan R., Xing M., Wang H.-H., Cui H.-E., Gong H.-B., Zhu H.-L. Synthesis, biological evaluation and molecular modeling of dihydro-pyrazolyl-thiazolinone derivatives as potential COX-2 inhibitors. Bioorg. Med. Chem. 2012;20:6648–6654.
doi: 10.1016/j.bmc.2012.09.021. [PubMed] [CrossRef] [Google Scholar]207. Alegaon S.G., Alagawadi K.R., Garg M.K., Dushyant K., Vinod D. 1,3,4-Trisubstituted pyrazole analogues as promising anti-inflammatory agents. Bioorg. Chem. 2014;54:51–59. doi: 10.1016/j.bioorg.2014.04.001. [PubMed] [CrossRef] [Google Scholar]208.
Hassan G.S., Abou-Seri S.M., Kamel G., Ali M.M. Celecoxib analogs bearing benzofuran moiety as cyclooxygenase-2 inhibitors: Design, synthesis and evaluation as potential anti-inflammatory agents. Eur. J. Med. Chem. 2014;76:482–493. doi: 10.1016/j.ejmech.2014.02.033. [PubMed] [CrossRef] [Google Scholar]209. Karrouchi K., Chemlal L., Doudach L., Taoufik J., Cherrah Y., Radi S., Fouzi M.A., Ansar M. Synthesis, anti-inflammatory and antioxidant activities of some new pyrazole derivatives. J. Pharm. Res. 2014;8:1171–1177. [Google Scholar]210. Selvam T.P., Kumar P.V., Saravanan G., Prakash C.R. Microwave-assisted synthesis, characterization and biological activity of novel pyrazole derivatives. J. Saudi Chem. Soc. 2014;18:1015–1021. doi: 10.1016/j.jscs.2011.12.006. [CrossRef] [Google Scholar]211. Tewari A.K., Singh V.P., Yadav P., Gupta G., Singh A., Goel R.K., Shinde P., Mohan C.G. Synthesis, biological evaluation and molecular modeling study of pyrazole derivatives as selective COX-2 inhibitors and anti-inflammatory agents. Bioorg. Chem. 2014;56:8–15. doi: 10.1016/j.bioorg.2014.05.004. [PubMed] [CrossRef] [Google Scholar]212. El-Feky S.A., El-Samii Z.K.A., Osman N.A., Lashine J., Kamel M.A., Thabet H.K. Synthesis, molecular docking and anti-inflammatory screening of novel quinoline incorporated pyrazole derivatives using the Pfitzinger reaction II.
Bioorg. Chem. 2015;58:104–116. doi: 10.1016/j.bioorg.2014.12.003. [PubMed] [CrossRef] [Google Scholar]213. Hussain S., Kaushik D. Noval 1-substituted-3,5-dimethyl-4-[(substituted phenyl)diazenyl] pyrazole derivatives: Synthesis and pharmacological activity.
J. Saudi Chem. Soc. 2015;19:274–281.
doi: 10.1016/j.jscs.2012.04.002. [CrossRef] [Google Scholar]214. Surendra Kumar R., Arif I.A., Ahamed A., Idhayadhulla A. Anti-inflammatory and antimicrobial activities of novel pyrazole analogues. Saudi J. Biol. Sci. 2016;23:614–620.
doi: 10.1016/j.sjbs.2015.07.005. [PMC free article] [PubMed] [CrossRef] [Google Scholar]215. Li Y.-R., Li C., Liu J.-C., Guo M., Zhang T.-Y., Sun L.-P., Zheng C.-J., Piao H.-R. Synthesis and biological evaluation of 1,3-diaryl pyrazole derivatives as potential antibacterial and anti-inflammatory agents. Bioorg. Med. Chem. Lett. 2015;25:5052–5057.
doi: 10.1016/j.bmcl.2015.10.028. [PubMed] [CrossRef] [Google Scholar]216. Pelcman B., Sanin A., Nilsson P., Schaal W., Olofsson K., Krog-Jensen C., Forsell P., Hallberg A., Larhed M., Boesend T., et al.
N-Substituted pyrazole-3-carboxamides as inhibitors of human 15-lipoxygenase. Bioorg. Med. Chem. Lett.
2015;25:3017–3023.
doi: 10.1016/j.bmcl.2015.05.007. [PubMed] [CrossRef] [Google Scholar]217. Wang T., Banerjee D., Bohnert T., Chao J., Enyedy I., Fontenot J., Guertina K., Jones H., Lina E.Y., Marcotte D., et al. Discovery of novel pyrazole-containing benzamides as potent RORγ inverse agonists. Bioorg. Med. Chem. Lett.
2015;25:2985–2990. doi: 10.1016/j.bmcl.2015.05.028. [PubMed] [CrossRef] [Google Scholar]218. Thore S., Gupta S.V., Baheti K.G. Novel ethyl-5-amino-3-methylthio-1H-pyrazole-4-carboxylates: Synthesis and pharmacological activity. J.
Saudi Chem. Sci. 2016;20:259–264. doi: 10.1016/j.jscs.2012.06.011. [CrossRef] [Google Scholar]219. Nossier E., Fahmy H., Khalifa N., El-Eraky W., Baset M. Design and Synthesis of Novel Pyrazole-Substituted Different Nitrogenous Heterocyclic Ring Systems as Potential Anti-Inflammatory Agents. Molecules. 2017;22:512.
doi: 10.3390/molecules22040512. [PMC free article] [PubMed] [CrossRef] [Google Scholar]220. Maggio B., Daidone G., Raffa D., Plescia S., Mantione L., Cutuli V.M.C., Mangano N.G., Caruso A.
Synthesis and pharmacological study of ethyl 1-methyl-5-(substituted 3,4-dihydro-4-oxoquinazolin-3-yl)-1H-pyrazole-4-acetates.
Eur. J. Med. Chem.
2001;36:737–742. doi: 10.1016/S0223-5234(01)01259-4. [PubMed] [CrossRef] [Google Scholar]221. Hall A., Billinton A., Brown S.H., Clayton N.M., Chowdhury A., Giblin G.M.P., Goldsmith P., Hayhow T.G., Hurst D.N., Kilford I.R., et al. Non-acidic pyrazole EP1 receptor antagonists with in vivo analgesic efficacy. Bioorg. Med. Chem. Lett. 2008;18:3392–3399.
doi: 10.1016/j.bmcl.2008.04.018. [PubMed] [CrossRef] [Google Scholar]222. De Moura S.S., de Ávila R.I., Brito L.B., de Oliveira R., de Oliveira G.A.R., Pazini F., Aline R.M., Cesar C.B., Marize K.G., Valadares C. In vitro genotoxicity and in vivo subchronic evaluation of the anti-inflammatory pyrazole compound LQFM021. Chem. Biol. Interact. 2017;277:185–194. doi: 10.1016/j.cbi.2017.09.004. [PubMed] [CrossRef] [Google Scholar]223. Ragab F.A., Abdel Gawad N.M., Georgey H.H., Said M.F. Synthesis of novel 1,3,4-trisubstituted pyrazoles as anti-inflammatory and analgesic agents.
Eur. J. Med. Chem. 2013;63:645–654.
doi: 10.1016/j.ejmech.2013.03.005. [PubMed] [CrossRef] [Google Scholar]224. Vijesh A.M., Isloor A.M., Shetty P., Sundershan S., Fun H.K. New pyrazole derivatives containing 1,2,4-triazoles and benzoxazoles as potent antimicrobial and analgesic agents. Eur. J. Med. Chem. 2013;62:410–415. doi: 10.1016/j.ejmech.2012.12.057. [PubMed] [CrossRef] [Google Scholar]225.
Viveka S., Dinesha S.P., Nagaraja G.K., Ballav S., Kerkar S. Design and synthesis of some new pyrazolyl-pyrazolines as potential anti-inflammatory, analgesic and antibacterial agents. Eur. J. Med. Chem. 2015;101:442–451. doi: 10.1016/j.ejmech.2015.07.002. [PubMed] [CrossRef] [Google Scholar]226. Thore S.N., Gupta S.V., Baheti K.G. Synthesis and pharmacological evaluation of 5-methyl-2-phenylthiazole-4-substituted heteroazoles as a potential anti-inflammatory and analgesic agents. J. Saudi Chem. Soc. 2016;20:S46–S52. doi: 10.1016/j.jscs.2012.09.002. [CrossRef] [Google Scholar]227. Chowdhury M.A., Abdellatif K.R., Dong Y., Knaus E.E. Synthesis of new 4-[2-(4-methyl(amino) sulfonylphenyl)-5-trifluoromethyl-2H-pyrazol-3-yl]-1,2,3,6-tetrahydropyridines: A search for novel nitric oxide donor anti-inflammatory agents. Bioorg. Med. Chem. 2008;16:8882–8888. doi: 10.1016/j.bmc.2008.08.059. [PubMed] [CrossRef] [Google Scholar]228.
Chowdhury M.A., Abdellatif K.R., Dong Y., Yu G., Huang Z., Rahman M., Das D., Velázquez C.A., Suresh M.R., Knaus E.E. Celecoxib analogs possessing a N-(4-nitrooxybutyl) piperidin-4-yl or N-(4-nitrooxybutyl)-1,2,3,6-tetrahydropyridin-4-yl nitric oxide donor moiety: Synthesis, biological evaluation and nitric oxide release studies. Bioorg. Med. Chem. Lett. 2010;20:1324–1329.
doi: 10.1016/j.bmcl.2010.01.014. [PubMed] [CrossRef] [Google Scholar]229. Chavan H.V., Bandgar B.P., Adsul L.K., Dhakane V.D., Bhale P.S., Thakare V.N., Masand V. Design, synthesis, characterization and anti-inflammatory evaluation of novel pyrazole amalgamated flavones. Bioorg. Med. Chem. Lett. 2013;23:1315–1321.
doi: 10.1016/j.bmcl.2012.12.094. [PubMed] [CrossRef] [Google Scholar]230.
Abdelgawad M.A., Labib L.B., Abdel-Latif M. Pyrazole-hydrazone derivatives as anti-inflammatory agents: Design, synthesis, biological evaluation, COX-1,2/5-LOX inhibition and docking study. Bioorg. Chem. 2017;74:212–220. doi: 10.1016/j.bioorg.2017.08.014. [PubMed] [CrossRef] [Google Scholar]231. Singh S.K., Reddy P.G., Rao K.S., Lohray B.B., Misra P., Rajjak S.A., Rao Y.K., Venkateswarlu A. Polar substitutions in the benzenesulfonamide ring of celecoxib afford a potent 1,5-diarylpyrazole class of COX-2 inhibitors. Bioorg. Med. Chem. Lett. 2004;14:499–504. doi: 10.1016/j.bmcl.2003.10.027. [PubMed] [CrossRef] [Google Scholar]232. Li J., DeMello K.M.L., Cheng H., Sakya S.M., Bronk B.S., Rafka R.J., Jaynes B.H., Ziegler C.B., Kilroy C., Mann D.W., et al. Discovery of a potent, selective and orally active canine COX-2 inhibitor, 2-(3-difluoromethyl-5-phenyl-pyrazol-1-yl)-5-methanesulfonyl-pyridine. Bioorg. Med. Chem. Lett. 2004;14:95–98. doi: 10.1016/j.bmcl.2003.10.004. [PubMed] [CrossRef] [Google Scholar]233. Cheng H., DeMello K.M.L., Li J., Sakya S.M., Ando K., Kawamura K., Kato T., Rafka R.J., Jaynes B.H., Ziegler C.B., et al. Synthesis and SAR of heteroaryl-phenyl-substituted pyrazole derivatives as highly selective and potent canine COX-2 inhibitors. Bioorg. Med. Chem. Lett. 2006;16:2076–2080. doi: 10.1016/j.bmcl.2006.01.059. [PubMed] [CrossRef] [Google Scholar]234. Sakya S.M., DeMello K.M.L., Minich M.L., Rast B., Shavnya A., Rafka R.J. 5-Heteroatom substituted pyrazoles as canine COX-2 inhibitors. Part 1: Structure-activity relationship studies of 5-alkylamino pyrazoles and discovery of a potent, selective, and orally active analog. Bioorg. Med. Chem. Lett. 2006;16:288–292. doi: 10.1016/j.bmcl.2005.10.006. [PubMed] [CrossRef] [Google Scholar]235. Sakya S.M., Cheng H., DeMello K.M.L., Shavnya A., Minich M.L., Rast B. 5-Heteroatom-substituted pyrazoles as canine COX-2 inhibitors: Part 2.
Structure-activity relationship studies of 5-alkylethers and 5-thioethers. Bioorg. Med. Chem. Lett. 2006;16:1202–1206. doi: 10.1016/j.bmcl.2005.11.110. [PubMed] [CrossRef] [Google Scholar]236. Aggarwal R., Bansal A., Rozas I., Kelly B., Kaushik P., Kaushik D. Synthesis, biological evaluation and molecular modeling study of 5-trifluoromethyl-Δ2-pyrazoline and isomeric 5/3-trifluoromethylpyrazole derivatives as anti-inflammatory agents. Eur. J. Med. Chem. 2013;70:350–357. doi: 10.1016/j.ejmech.2013.09.052.
[PubMed] [CrossRef] [Google Scholar]237.
Habeeb A.G., Praveen R.P., Knaus E.E. Design and synthesis of celecoxib and rofecoxib analogues as selective cyclooxygenase-2 (COX-2) inhibitors: Replacement of sulfonamide and methylsulfonyl pharmacophores by an azido bioisostere. J. Med. Chem. 2001;44:3039–3042.
doi: 10.1021/jm010153c. [PubMed] [CrossRef] [Google Scholar]238.
Uddin M.J., Rao P.P., Knaus E.E. Design and synthesis of novel celecoxib analogues as selective cyclooxygenase-2 (COX-2) inhibitors: Replacement of the sulfonamide pharmacophore by a sulfonylazide bioisostere. Bioorg. Med. Chem. 2003;11:5273–5280. doi: 10.1016/j.bmc.2003.07.005. [PubMed] [CrossRef] [Google Scholar]239. Bansal S., Bala M., Suthar S.K., Choudhary S., Bhattacharya S., Bhardwaj V. Design and synthesis of novel 2-phenyl-5-(1,3-diphenyl-1H-pyrazol-4-yl)-1,3,4-oxadiazoles as selective COX-2 inhibitors with potent anti-inflammatory activity. Eur. J. Med.
Chem. 2014;80:167–174. doi: 10.1016/j.ejmech.2014.04.045. [PubMed] [CrossRef] [Google Scholar]240. El-Sayed M.A.A., Abdel-Aziz N.I., Abdel-Aziz A.A.M., El-Azab A.S., Asiri Y.A., ElTahir K.E.H. Design, synthesis, and biological evaluation of substituted hydrazone and pyrazole derivatives as selective COX-2 inhibitors: Molecular docking study. Bioorg. Med. Chem. 2011;19:3416–3424. doi: 10.1016/j.bmc.2011.04.027. [PubMed] [CrossRef] [Google Scholar]241. Bekhit A.A., Ashour H.M., Bekhit A.E.D.A., Abdel-Rahman H.M., Bekhit S.A. Synthesis of some pyrazolyl benzenesulfonamide derivatives as dual anti-inflammatory antimicrobial agents. J. Enzym. Inhib.
Med. Chem.
2009;24:296–309. doi: 10.1080/14756360802188404. [PubMed] [CrossRef] [Google Scholar]242. Tewari A.K., Srivastava P., Singh V.P., Singh A., Goel R.K., Mohan C.G. Novel anti-inflammatory agents based on pyrazole based dimeric compounds; design, synthesis, docking and in vivo activity. Chem. Pharm. Bull. 2010;58:634–638.
doi: 10.1248/cpb.58.634. [PubMed] [CrossRef] [Google Scholar]243. Alegaon S.G., Hirpara M.B., Alagawadi K.R., Hullatti K.K., Kashniyal K. Synthesis of novel pyrazole–thiadiazole hybrid as potential potent and selective cyclooxygenase-2 (COX-2) inhibitors. Bioorg. Med. Chem. Lett.
2014;24:5324–5329. doi: 10.1016/j.bmcl.2014.08.062. [PubMed] [CrossRef] [Google Scholar]244. Manetti F., Magnani M., Castagnolo D., Passalacqua L., Botta M., Corelli F. Ligand-Based Virtual Screening, Parallel Solution-Phase and Microwave-Assisted Synthesis as Tools to Identify and Synthesize New Inhibitors of Mycobacterium tuberculosis. Chem.
Med. Chem. 2006;1:973–989. doi: 10.1002/cmdc.200600026.
[PubMed] [CrossRef] [Google Scholar]245. Almeida P.E., Ramos D.F., Bonacorso H.G., de la Iglesia A.I., Oliveira M.R., Coelho T.
Synthesis and in vitro antimycobacterial activity of 3-substituted 5-hydroxy-5-trifluoro[chloro]methyl-4,5-dihydro-1H-1-(isonicotinoyl)pyrazoles. Int. J. Antimicrob. Agents. 2008;32:139–144. doi: 10.1016/j.ijantimicag.2008.03.019. [PubMed] [CrossRef] [Google Scholar]246. Castagnolo D., De Logu A., Radi M., Bechi B., Manetti F., Magnani M. Synthesis, biological evaluation and SAR study of novel pyrazole analogues as inhibitors of Mycobacterium tuberculosis. Bioorg. Med. Chem. 2008;16:8587–85891.
doi: 10.1016/j.bmc.2008.08.016. [PubMed] [CrossRef] [Google Scholar]247. Velaparthi S., Brunsteiner M., Uddin R., Wan B., Franzblau S.G., Petukhov P.A. 5-tert-Butyl-N-pyrazol-4-yl-4,5,6,7-tetrahydrobenzo[d]isoxazole-3-carboxamide derivatives as novel potent inhibitors of Mycobacterium tuberculosis pantothenate synthetase: Initiating a quest for new antitubercular drugs. J. Med. Chem. 2008;51:1999–2002. doi: 10.1021/jm701372r.
[PubMed] [CrossRef] [Google Scholar]248. Castagnolo D., Manetti F., Radi M., Bechi B., Pagano M., De Logu A., Meleddu R., Saddi M., Botta M.
Synthesis, biological evaluation, and SAR study of novel pyrazole analogues as inhibitors of Mycobacterium tuberculosis: Part 2. Synthesis of rigid pyrazolones. Bioorg. Med. Chem. 2009;17:5716–5721. doi: 10.1016/j.bmc.2009.05.058. [PubMed] [CrossRef] [Google Scholar]249. Ahsan M.J., Samy J.G., Soni S., Jain N., Kumar L., Sharma L.K., Yadav H., Saini L., Kalyansing R.G., Devenda N.S. Discovery of novel antitubercular 3a,4-dihydro-3H-indeno[1,2-c]pyrazole-2-carboxamide/carbothioamide analogues. Bioorg. Med. Chem. Lett. 2011;21:5259–5261. doi: 10.1016/j.bmcl.2011.07.035. [PubMed] [CrossRef] [Google Scholar]250. Trivedi A.R., Dodiya D.K., Dholariya B.H., Kataria V.B., Bhuva V.R., Shah V.H. Synthesis and biological evaluation of some novel N-aryl-1,4-dihydropyridines as potential antitubercular agents. Bioorg. Med. Chem. Lett. 2011;21:5181–5183. doi: 10.1016/j.bmcl.2011.07.068. [PubMed] [CrossRef] [Google Scholar]251.
Khunt R.C., Khedkar V.M., Chawda R.S., Chauhan N.A., Parikh A.R., Coutinho E.C. Synthesis, antitubercular evaluation and 3D-QSAR study of N-phenyl-3-(4-fluorophenyl)-4-substituted pyrazole derivatives. Bioorg. Med. Chem. Lett. 2012;22:666–678.
doi: 10.1016/j.bmcl.2011.10.059. [PubMed] [CrossRef] [Google Scholar]252. Shelke S.N., Mhaske G.R., Bonifácio V.D., Gawande M.B. Green synthesis and anti-infective activities of fluorinated pyrazoline derivatives. Bioorg. Med. Chem. Lett. 2012;22:5727–5730. doi: 10.1016/j.bmcl.2012.06.072. [PubMed] [CrossRef] [Google Scholar]253.
Anand N., Ramakrishna K., Gupt M.P., Chaturvedi V., Singh S., Srivastava K.K., Sharma P., Rai N., Ramachandran R., Dwivedi A. Identification of 1-[4-benzyloxyphenyl)-but-3-enyl]-1H-azoles as new class of antitubercular and antimicrobial agents. ACS Med. Chem. Lett. 2013;4:958–963. doi: 10.1021/ml4002248. [PMC free article] [PubMed] [CrossRef] [Google Scholar]254. Fullam E., Talbot J., Abuhammed A., Westwood I., Davies S.G., Russell A.J., Sim E. Design, synthesis and structure-activity relationships of 3,5-diaryl-1H-pyrazoles as inhibitors of arylamine N-acetyltransferase. Bioorg.
Med. Chem. Lett. 2013;23:2759–2764. doi: 10.1016/j.bmcl.2013.02.052. [PubMed] [CrossRef] [Google Scholar]255. Hernández P., Rojas R., Gilman R.H., Sauvain M., Lima L.M., Barreiro E.J., González M., Cerecetto H. Hybrid furoxanyl N-acylhydrazone derivatives as hits for the development of neglected diseases drug candidates. Eur.
J. Med. Chem. 2013;59:64–74. doi: 10.1016/j.ejmech.2012.10.047. [PubMed] [CrossRef] [Google Scholar]256. Maurya H.K., Verma R., Alam S., Pandey S., Pathak V., Sharma S., Srivastava K.K., Negi A.S., Gupta A. Studies on substituted benzo[h]quinazolines, benzo[g]indazoles, pyrazoles, 2,6-diarylpyridines as anti-tubercular agents. Bioorg. Med. Chem. Lett. 2013;23:5844–5849. doi: 10.1016/j.bmcl.2013.08.101. [PubMed] [CrossRef] [Google Scholar]257. North E.J., Scherman M.S., Bruhn D.F., Scarborough J.S., Maddox M.M., Jones V., Grzegorzewicz A., Yang L., Hess T., Morisseau C. Design, synthesis and anti-tuberculosis activity of 1-adamantyl-3-heteroaryl ureas with improved in vitro pharmacokinetic properties. Bioorg. Med. Chem. 2013;21:2587–2599. doi: 10.1016/j.bmc.2013.02.028.
[PMC free article] [PubMed] [CrossRef] [Google Scholar]258. Palanisamy P., Jenniefer S.J., Muthiah P.T., Kumaresan S. Synthesis, characterization, antimicrobial, anticancer, and antituberculosis activity of some new pyrazole, isoxazole, pyrimidine and benzodiazepine derivatives containing thiochromeno and benzothiepino moieties.
RSC Adv. 2013;3:19300–19310.
doi: 10.1039/c3ra42283f.
[CrossRef] [Google Scholar]259. Samala G., Devi P.B., Nallangi R., Yogeeswari P., Sriram D. Development of 3-phenyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine derivatives as novel Mycobacterium tuberculosis pantothenate synthetase inhibitors. Eur. J. Med. Chem. 2013;69:356–364. doi: 10.1016/j.ejmech.2013.08.036. [PubMed] [CrossRef] [Google Scholar]260. Shirude P.S., Madhavapeddi P., Naik M., Murugan K., Shinde V., Nandishaiah R., Bhat J., Kumar A., Hameed S., Holdgate G. Methyl-thiazoles: A novel mode of inhibition with the potential to develop novel inhibitors targeting InhA in Mycobacterium tuberculosis. J.
Med.
Chem. 2013;56:8533–8542. doi: 10.1021/jm4012033. [PubMed] [CrossRef] [Google Scholar]261. Kalaria P.N., Satasia S.P., Raval D.K. Synthesis, characterization and pharmacological screening of some novel 5-imidazopyrazole incorporated polyhydroquinoline derivatives. Eur. J. Med. Chem. 2014;78:207–216. doi: 10.1016/j.ejmech.2014.02.015. [PubMed] [CrossRef] [Google Scholar]262. Karad S.C., Purohit V.B., Raval D.K. Design, synthesis and characterization of fluoro substituted novel pyrazolylpyrazolines scaffold and their pharmacological screening. Eur. J. Med. Chem. 2014;84:51–58. doi: 10.1016/j.ejmech.2014.07.008. [PubMed] [CrossRef] [Google Scholar]263.
Pathak V., Maurya H.K., Sharma S., Srivastava K.K., Gupta A. Synthesis and biological evaluation of substituted 4,6-diarylpyrimidines and 3,5-diphenyl-4,5-dihydro-1H-pyrazoles as anti-tubercular agents. Bioorg. Med.
Chem. Lett. 2014;24:2892–2896. doi: 10.1016/j.bmcl.2014.04.094. [PubMed] [CrossRef] [Google Scholar]264. Villemagne B., Flipo M., Blondiaux N., Crauste C., Malaquin S., Leroux F., Piveteau C., Villeret V., Brodin P., Villoutreix B.O., et al. Ligand Efficiency Driven Design of New Inhibitors of Mycobacterium tuberculosis Transcriptional Repressor EthR Using Fragment Growing, Merging, and Linking Approaches. J. Med. Chem. 2014;57:4876–4888. doi: 10.1021/jm500422b. [PubMed] [CrossRef] [Google Scholar]265. Bhatt J.D., Chudasama C.J., Patel K.D. Pyrazole clubbed triazolo[1,5-a]pyrimidine hybrids as an anti-tubercular agents: Synthesis, in vitro screening and molecular docking study. Bioorg. Med. Chem. 2015;23:7711–7716. doi: 10.1016/j.bmc.2015.11.018.
[PubMed] [CrossRef] [Google Scholar]266.
Da Silva C., Ribeiro L.B., Furuno C.C., da Cunha G.A., de Souza R.F., Netto A.V., Mauro A.E., Frem R.C., Fernandes J.A., Paz F.A.A. Pyrazolyl Pd (II) complexes containing triphenylphosphine: Synthesis and antimycobacterial activity. Polyhedron. 2015;100:10–16. doi: 10.1016/j.poly.2015.07.009. [CrossRef] [Google Scholar]267. De Melo C.S., Feng T.-S., van der Westhuyzen R., Gessner R.K., Street L.J., Morgans G.L., Warner D.F., Moosa A., Naran K., Lawrence N. Aminopyrazolo[1,5-a]pyrimidines as potential inhibitors of Mycobacterium tuberculosis: Structure activity relationships and ADME characterization. Bioorg. Med. Chem. 2015;23:7240–7250. doi: 10.1016/j.bmc.2015.10.021. [PubMed] [CrossRef] [Google Scholar]268. Mutai P., Pavadai E., Wiid I., Ngwane A., Baker B., Chibale K. Synthesis, antimycobacterial evaluation and pharmacophore modeling of analogues of the natural product formononetin. Bioorg. Med. Chem. Lett. 2015;25:2510–2513. doi: 10.1016/j.bmcl.2015.04.064. [PubMed] [CrossRef] [Google Scholar]269. Nayak N., Ramprasad J., Dalimba U. New INH-pyrazole analogs: Design, synthesis and evaluation of antitubercular and antibacterial activity.
Bioorg. Med. Chem. Lett. 2015;25:5540–5545. doi: 10.1016/j.bmcl.2015.10.057. [PubMed] [CrossRef] [Google Scholar]270. Tantry S.J., Degiacomi G., Sharma S., kumar Jena L., Narayan A., Guptha S., Shanbhag G., Menasinakai S., Mallya M., Awasthy D. Whole cell screen based identification of spiropiperidines with potent antitubercular properties. Bioorg. Med. Chem.
Lett. 2015;25:3234–3245. doi: 10.1016/j.bmcl.2015.05.087. [PubMed] [CrossRef] [Google Scholar]271. Guardia A., Gulten G., Fernandez R., Gómez J., Wang F., Convery M., Blanco D., Martínez M., Pérez-Herrán E., Alonso M. N-Benzyl-4-((heteroaryl)methyl) benzamides: A New Class of Direct NADH-Dependent 2-trans Enoyl–Acyl Carrier Protein Reductase (InhA) Inhibitors with Antitubercular Activity. Chem.
Med.
Chem. 2016;11:687–701. doi: 10.1002/cmdc.201600020. [PubMed] [CrossRef] [Google Scholar]272. Kavanagh M.E., Coyne A.G., McLean K.J., James G.G., Levy C.W., Marino L.B., De Carvalho L.P.S., Chan D.S., Hudson S.A., Surade S.
Fragment-based approaches to the development of Mycobacterium tuberculosis CYP121 inhibitors. J. Med. Chem. 2016;59:3272–3302.
doi: 10.1021/acs.jmedchem.6b00007. [PMC free article] [PubMed] [CrossRef] [Google Scholar]273. Lu X., Tang J., Liu Z., Li M., Zhang T., Zhang X., Ding K. Discovery of new chemical entities as potential leads against Mycobacterium tuberculosis. Bioorg. Med. Chem. Lett. 2016;26:5916–5919.
doi: 10.1016/j.bmcl.2016.11.003. [PubMed] [CrossRef] [Google Scholar]274.
Nayak N., Ramprasad J., Dalimba U. Synthesis and antitubercular and antibacterial activity of some active fluorine containing quinoline–pyrazole hybrid derivatives. J.
Fluor. Chem.
2016;183:59–68. doi: 10.1016/j.jfluchem.2016.01.011. [CrossRef] [Google Scholar]275. Ramesh R., Shingare R.D., Kumar V., Anand A., Swetha B., Veeraraghavan S., Viswanadha S., Ummanni R., Gokhale R., Reddy D.S. Repurposing of a drug scaffold: Identification of novel sila analogues of rimonabant as potent antitubercular agents. Eur. J. Med. Chem. 2016;122:723–730. doi: 10.1016/j.ejmech.2016.07.009. [PubMed] [CrossRef] [Google Scholar]276. Amaroju S., Kalaga M.N., Srinivasarao S., Napiorkowska A., Augustynowicz-Kopec E., Murugesan S., Chander S., Krishnan R., Chandra Sekhar K.V.G. Identification and development of pyrazolo[4,3-c]pyridine carboxamides as Mycobacterium tuberculosis pantothenate synthetase inhibitors. New J. Chem. 2017;41:347–357. doi: 10.1039/C6NJ02671K. [CrossRef] [Google Scholar]277. Angelova V.T., Valcheva V., Pencheva T., Voynikov Y., Vassilev N., Mihaylova R., Momekov G., Shivachev B. Synthesis, antimycobacterial activity and docking study of 2-aroyl-[1]benzopyrano[4,3-c]pyrazol-4(1H)-one derivatives and related hydrazide-hydrazones. Bioorg. Med. Chem. Lett. 2017;27:2996–3002. doi: 10.1016/j.bmcl.2017.05.011. [PubMed] [CrossRef] [Google Scholar]278. He C., Preiss L., Wang B., Fu L., Wen H., Zhang X., Cui H., Meier T., Yin D. Structural Simplification of Bedaquiline: The Discovery of 3-(4-(N,N-Dimethylaminomethyl)phenyl) quinoline-Derived Antitubercular Lead Compounds. Chem. Med. Chem. 2017;12:106–119. doi: 10.1002/cmdc.201600441. [PMC free article] [PubMed] [CrossRef] [Google Scholar]279. Aragade P., Palkar M., Ronad P., Satyanarayana D. Coumarinyl pyrazole derivatives of INH: Promising antimycobacterial agents. Med. Chem. Res. 2013;22:2279–2283. doi: 10.1007/s00044-012-0222-8. [CrossRef] [Google Scholar]280. Gajbhiye J., More N., Patil M.D., Ummanni R., Kotapalli S., Yogeeswari P., Sriram D., Masand V.
Discovery of Rimonabant and its potential analogues as anti-TB drug candidates. Med. Chem.
Res. 2015;24:2960–2971. doi: 10.1007/s00044-015-1346-4. [CrossRef] [Google Scholar]281. Nayak N., Ramprasad J., Dalimba U. Design, Synthesis, and Biological Evaluation of New 8-Trifluoromethylquinoline Containing Pyrazole-3-carboxamide Derivatives. J. Heterocycl. Chem. 2017;54:171–182. doi: 10.1002/jhet.2564. [CrossRef] [Google Scholar]282. Trivedi A.R., Dholariya B.H., Vakhariya C.P., Dodiya D.K., Ram H.K., Kataria V.B., Siddiqui A.B., Shah V.H. Synthesis and anti-tubercular evaluation of some novel pyrazolo[3,4-d]pyrimidine derivatives. Med. Chem. Res. 2012;21:1887–1891. doi: 10.1007/s00044-011-9712-3. [CrossRef] [Google Scholar]283. Labana B.M., Brahmbhatt G.C., Sutariya T.R., Parmar N.J., Padrón J.M., Kant R., Gupta V.K. Efficient synthesis and biological evaluation of new benzopyran-annulated pyrano[2,3-c]pyrazole derivatives. Mol. Divers. 2017;21:339–354.
doi: 10.1007/s11030-017-9734-y. [PubMed] [CrossRef] [Google Scholar]284. Encinas L., O'Keefe H., Neu M., Remuiñán M.J., Patel A.M., Guardia A., Davie C.P., Pérez-Macías N., Yang H., Convery M.A. Encoded library technology as a source of hits for the discovery and lead optimization of a potent and selective class of bactericidal direct inhibitors of Mycobacterium tuberculosis InhA. J. Med. Chem. 2014;57:1276–1288. doi: 10.1021/jm401326j. [PubMed] [CrossRef] [Google Scholar]285.
Rachakonda V., Alla M., Kotipalli S.S., Ummani R. Design, diversity-oriented synthesis and structure activity relationship studies of quinolinyl heterocycles as antimycobacterial agents. Eur. J. Med. Chem. 2013;70:536–547.
doi: 10.1016/j.ejmech.2013.10.034. [PubMed] [CrossRef] [Google Scholar]286. Pandit U., Dodiya A. Synthesis and antitubercular activity of novel pyrazole–quinazolinone hybrid analogs. Med.
Chem. Res. 2013;22:3364–3371. doi: 10.1007/s00044-012-0351-0. [CrossRef] [Google Scholar]287. Mistry P.T., Kamdar N.R., Haveliwala D.D., Patel S.K. Synthesis, characterization, and in vitro biological studies of some novel pyran fused pyrimidone derivatives. J.
Heterocycl. Chem. 2012;49:349–357. doi: 10.1002/jhet.700. [CrossRef] [Google Scholar]288. Naik M., Humnabadkar V., Tantry S.J., Panda M., Narayan A., Guptha S., Panduga V., Manjrekar P., Jena L.K., Koushik K. 4-aminoquinolone piperidine amides: Noncovalent inhibitors of DprE1 with long residence time and potent antimycobacterial activity. J. Med. Chem. 2014;57:5419–5434. doi: 10.1021/jm5005978.
[PubMed] [CrossRef] [Google Scholar]289. Manfredini S., Bazzanini R., Baraldi P.G., Guarneri M., Simoni D., Marongiu M.E., Pani A., La Colla P., Tramontano E. Pyrazole-related nucleosides. Synthesis and antiviral/antitumor activity of some substituted pyrazole and pyrazolo[4,3-d]-1,2,3-triazin-4-one nucleosides. J. Med. Chem. 1992;35:917–924.
doi: 10.1021/jm00083a017. [PubMed] [CrossRef] [Google Scholar]290. Chen X., Schneller S.W., Ikeda S., Snoeck R., Andrei G., Balzarini J., De Clercq E. Synthesis and antiviral activity of 5′-deoxypyrazofurin. J. Med. Chem.
1993;36:3727–3730. doi: 10.1021/jm00075a030. [PubMed] [CrossRef] [Google Scholar]291. Storer R., Ashton C.J., Baxter A.D., Hann M.M., Marr C.L.P., Mason A.M., Mo C.-L., Myers P.L., Noble S.A., Penn C.R., et al. The Synthesis and Antiviral Activity of 4-Fluoro-1-β-d-ribofuranosyl-1H-pyrazole-3-carboxamide. Nucleosides Nucleotides. 1999;18:203–216. doi: 10.1080/15257779908043068. [PubMed] [CrossRef] [Google Scholar]292. Genin M.J., Biles C., Keiser B.J., Poppe S.M., Swaney S.M., Tarpley W.G., Yagi Y., Romero D.L. Novel 1,5-Diphenylpyrazole Nonnucleoside HIV-1 Reverse Transcriptase Inhibitors with Enhanced Activity versus the Delavirdine-Resistant P236L Mutant: Lead Identification and SAR of 3- and 4-Substituted Derivatives. J. Med. Chem. 2000;43:1034–1040.
doi: 10.1021/jm990383f.
[PubMed] [CrossRef] [Google Scholar]293. Rostom S.A.F., Shalaby M.A., El-Demellawy M.A. Polysubstituted pyrazoles, part 5. Synthesis of new 1-(4-chlorophenyl)-4-hydroxy-1H-pyrazole-3-carboxylic acid hydrazide analogs and some derived ring systems. A novel class of potential antitumor and anti-HCV agents. Eur. J. Med. Chem. 2003;38:959–974.
doi: 10.1016/j.ejmech.2003.08.003. [PubMed] [CrossRef] [Google Scholar]294.
Shamroukh A.H., Zaki M.E., Morsy E.M., Abdel-Motti F.M., Abdel-Megeid F.M. Synthesis of Pyrazolo [4′,3′:5,6] pyrano[2,3-d]pyrimidine Derivatives for Antiviral Evaluation. Arch. Pharm. 2007;340:236–243. doi: 10.1002/ardp.200700005. [PubMed] [CrossRef] [Google Scholar]295. Sun A., Chandrakumar N., Yoon J.-J., Plemper R.K., Snyder J.P. Non-nucleoside inhibitors of the measles virus RNA-dependent RNA polymerase complex activity: Synthesis and in vitro evaluation. Bioorg. Med. Chem. Lett. 2007;17:5199–5203. doi: 10.1016/j.bmcl.2007.06.084. [PMC free article] [PubMed] [CrossRef] [Google Scholar]296. Ouyang G., Chen Z., Cai X.-J., Song B.-A., Bhadury P.S., Yang S., Jin L.-H., Xue W., Hu D.-Y., Zeng S. Synthesis and antiviral activity of novel pyrazole derivatives containing oxime esters group. Bioorg. Med. Chem. 2008;16:9699–9707. doi: 10.1016/j.bmc.2008.09.070. [PubMed] [CrossRef] [Google Scholar]297. Rashad A.E., Hegab M.I., Abdel-Megeid R.E., Micky J.A., Abdel-Megeid F.M. Synthesis and antiviral evaluation of some new pyrazole and fused pyrazolopyrimidine derivatives. Bioorg. Med. Chem. 2008;16:7102–7106. doi: 10.1016/j.bmc.2008.06.054. [PubMed] [CrossRef] [Google Scholar]298. Zeng L.-F., Zhang H.-S., Wang Y.-H., Sanchez T., Zheng Y.-T., Neamati N., Long Y.-Q. Efficient synthesis and utilization of phenyl-substituted heteroaromatic carboxylic acids as aryl diketo acid isosteres in the design of novel HIV-1 integrase inhibitors. Bioorg. Med. Chem. Lett. 2008;18:4521–4524. doi: 10.1016/j.bmcl.2008.07.047. [PubMed] [CrossRef] [Google Scholar]299. Mowbray C.E., Burt C., Corbau R., Gayton S., Hawes M., Perros M., Tran I., Price D.A., Quinton F.J., Selby M.D. Pyrazole NNRTIs 4: Selection of UK-453,061 (lersivirine) as a development candidate. Bioorg. Med. Chem. Lett. 2009;19:5857–5860. doi: 10.1016/j.bmcl.2009.08.080. [PubMed] [CrossRef] [Google Scholar]300.
Mowbray C.E., Burt C., Corbau R., Perros M., Tran I., Stupple P.A., Webster R., Wood A. Pyrazole NNRTIs 1: Design and initial optimisation of a novel template. Bioorg. Med. Chem. Lett. 2009;19:5599–5602. doi: 10.1016/j.bmcl.2009.08.039. [PubMed] [CrossRef] [Google Scholar]301. Sidique S., Shiryaev S.A., Ratnikov B.I., Herath A., Su Y., Strongin A.Y., Cosford N.D. Structure–activity relationship and improved hydrolytic stability of pyrazole derivatives that are allosteric inhibitors of West Nile Virus NS2B-NS3 proteinase. Bioorg. Med. Chem. Lett. 2009;19:5773–5777.
doi: 10.1016/j.bmcl.2009.07.150. [PMC free article] [PubMed] [CrossRef] [Google Scholar]302. Sujatha K., Shanthi G., Selvam N.P., Manoharan S., Perumal P.T., Rajendran M. Synthesis and antiviral activity of 4,4′-(arylmethylene)bis(1H-pyrazol-5-ols) against peste des petits ruminant virus (PPRV) Bioorg. Med. Chem. Lett. 2009;19:4501–4503.
doi: 10.1016/j.bmcl.2009.02.113. [PubMed] [CrossRef] [Google Scholar]303. Riyadh S.M., Farghaly T.A., Abdallah M.A., Abdalla M.M., El-Aziz M.R.A. New pyrazoles incorporating pyrazolylpyrazole moiety: Synthesis, anti-HCV and antitumor activity. Eur. J. Med. Chem. 2010;45:1042–1050. doi: 10.1016/j.ejmech.2009.11.050. [PubMed] [CrossRef] [Google Scholar]304.
Shih S.-R., Chu T.-Y., Reddy G.R., Tseng S.-N., Chen H.-L., Tang W.-F., Wu M.-S., Yeh J.-Y., Chao Y.-S., Hsu J.T. Pyrazole compound BPR1P0034 with potent and selective anti-influenza virus activity. J. Biomed. Sci. 2010;17:13–21. doi: 10.1186/1423-0127-17-13. [PMC free article] [PubMed] [CrossRef] [Google Scholar]305. Su D.-S., Lim J.J., Tinney E., Tucker T.J., Saggar S., Sisko J.T., Wan B.-L., Young M.B., Anderson K.D., Rudd D. Biaryl ethers as potent allosteric inhibitors of reverse transcriptase and its key mutant viruses: Aryl substituted pyrazole as a surrogate for the pyrazolopyridine motif. Bioorg. Med. Chem. Lett. 2010;20:4328–4332. doi: 10.1016/j.bmcl.2010.06.083. [PubMed] [CrossRef] [Google Scholar]306. Dawood K.M., Abdel-Gawad H., Mohamed H.A., Badria F.A. Synthesis, anti-HSV-1, and cytotoxic activities of some new pyrazole-and isoxazole-based heterocycles. Med. Chem. Res. 2011;20:912–919. doi: 10.1007/s00044-010-9420-4. [CrossRef] [Google Scholar]307. Wu L., Song B., Bhadury P.S., Yang S., Hu D., Jin L.
Synthesis and antiviral activity of novel pyrazole amides containing α-aminophosphonate moiety. J. Heterocycl. Chem. 2011;48:389–396. doi: 10.1002/jhet.591. [CrossRef] [Google Scholar]308. Di Francesco M.E., Avolio S., Pompei M., Pesci S., Monteagudo E., Pucci V., Giuliano C., Fiore F., Rowley M., Summa V. Synthesis and antiviral properties of novel 7-heterocyclic substituted 7-deaza-adenine nucleoside inhibitors of Hepatitis C NS5B polymerase. Bioorg. Med. Chem. 2012;20:4801–4811. doi: 10.1016/j.bmc.2012.05.067. [PubMed] [CrossRef] [Google Scholar]309. Kim J., Lee D., Park C., So W., Jo M., Ok T., Kwon J., Kong S., Jo S., Kim Y. Discovery of phenylaminopyridine derivatives as novel HIV-1 non-nucleoside reverse transcriptase inhibitors. ACS Med. Chem. Lett. 2012;3:678–682. doi: 10.1021/ml300146q. [PMC free article] [PubMed] [CrossRef] [Google Scholar]310. Ndungu J.M., Krumm S.A., Yan D., Arrendale R.F., Reddy G.P., Evers T., Howard R., Natchus M.G., Saindane M.T., Liotta D.C. Non-nucleoside inhibitors of the measles virus RNA-dependent RNA polymerase: Synthesis, structure-activity relationships, and pharmacokinetics.
J. Med. Chem. 2012;55:4220–4230. doi: 10.1021/jm201699w. [PMC free article] [PubMed] [CrossRef] [Google Scholar]311. Tantawy A.S., Nasr M.N., El-Sayed M.A., Tawfik S.S. Synthesis and antiviral activity of new 3-methyl-1,5-diphenyl-1H-pyrazole derivatives. Med. Chem. Res. 2012;21:4139–4149.
doi: 10.1007/s00044-011-9960-2. [CrossRef] [Google Scholar]312. Zhang D.Q., Xu G.F., Fan Z.J., Wang D.Q., Yang X.L., Yuan D.K. Synthesis and anti-TMV activity of novel N-(3-alkyl-1H-pyrazol-4-yl)-3-alkyl-4-substituted-1H-pyrazole-5-carboxamides. Chin. Chem. Lett. 2012;23:669–672. doi: 10.1016/j.cclet.2012.04.010. [CrossRef] [Google Scholar]313. Hwang J.Y., Kim H.-Y., Park D.-S., Choi J., Baek S.M., Kim K., Kim S., Seong S., Choi I., Lee H.-G. Identification of a series of 1,3,4-trisubstituted pyrazoles as novel hepatitis C virus entry inhibitors. Bioorg. Med. Chem. Lett. 2013;23:6467–6473. doi: 10.1016/j.bmcl.2013.09.039. [PubMed] [CrossRef] [Google Scholar]314. Mizuhara T., Kato T., Hirai A., Kurihara H., Shimada Y., Taniguchi M., Maeta H., Togami H., Shimura K., Matsuoka M. Structure-activity relationship study of phenylpyrazole derivatives as a novel class of anti-HIV agents. Bioorg. Med. Chem. Lett. 2013;23:4557–4561. doi: 10.1016/j.bmcl.2013.06.026.
[PubMed] [CrossRef] [Google Scholar]315.
Moreau B., O'Meara J.A., Bordeleau J.E., Garneau M., Godbout C., Gorys V., Leblanc M.L., Villemure E., White P.W., Llinàs-Brunet M. Discovery of hepatitis C virus NS3-4A protease inhibitors with improved barrier to resistance and favorable liver distribution. J. Med. Chem. 2013;57:1770–1776. doi: 10.1021/jm400121t. [PubMed] [CrossRef] [Google Scholar]316. Bhadoriya K.S., Sharma M.C., Jain S.V. 2,4-Dihydropyrano[2,3-c]pyrazole: Discovery of new lead as through pharmacophore modelling, atom-based 3D-QSAR, virtual screening and docking strategies for improved anti-HIV-1 chemotherapy. J. Taibah Univ. Sci. 2015;9:521–530.
doi: 10.1016/j.jtusci.2014.12.005. [CrossRef] [Google Scholar]317. Fioravanti R., Desideri N., Biava M., Droghini P., Atzori E.M., Ibba C., Collu G., Sanna G., Delogu I., Loddo R. N-((1,3-Diphenyl-1H-pyrazol-4-yl)methyl) anilines: A novel class of anti-RSV agents. Bioorg. Med. Chem. Lett. 2015;25:2401–2404.
doi: 10.1016/j.bmcl.2015.04.006. [PubMed] [CrossRef] [Google Scholar]318. Han C., Guo Y.-C., Wang D.-D., Dai X.-J., Wu F.-J., Liu H.-F., Dai G.-F., Tao J.-C. Novel pyrazole fused heterocyclic ligands: Synthesis, characterization, DNA binding/cleavage activity and anti-BVDV activity. Chin. Chem.
Lett. 2015;26:534–538. doi: 10.1016/j.cclet.2015.01.006. [CrossRef] [Google Scholar]319. Manvar D., Pelliccia S., La Regina G., Famiglini V., Coluccia A., Ruggieri A., Anticoli S., Lee J.-C., Basu A., Cevik O. New 1-phenyl-5-(1H-pyrrol-1-yl)-1H-pyrazole-3-carboxamides inhibit hepatitis C virus replication via suppression of cyclooxygenase-2. Eur. J. Med. Chem. 2015;90:497–506. doi: 10.1016/j.ejmech.2014.11.042. [PubMed] [CrossRef] [Google Scholar]320. Chuang H., Huang L.-C.S., Kapoor M., Liao Y.-J., Yang C.-L., Chang C.-C., Wu C.-Y., Hwu J.R., Huang T.-J., Hsu M.-H. Design and synthesis of pyridine-pyrazole-sulfonate derivatives as potential anti-HBV agents. MedChemComm. 2016;7:832–836. doi: 10.1039/C6MD00008H. [CrossRef] [Google Scholar]321. Ouyang G., Cai X.-J., Chen Z., Song B.-A., Bhadury P.S., Yang S., Jin L.-H., Xue W., Hu D.-Y., Zeng S.
Synthesis and Antiviral Activities of Pyrazole Derivatives Containing an Oxime Moiety. J. Agric. Food Chem.
2008;56:10160–10167. doi: 10.1021/jf802489e. [PubMed] [CrossRef] [Google Scholar]322. Jia H., Bai F., Liu N., Liang X., Zhan P., Ma C., Jiang X., Liu X. Design, synthesis and evaluation of pyrazole derivatives as non-nucleoside hepatitis B virus inhibitors. Eur. J. Med. Chem. 2016;123:202–210. doi: 10.1016/j.ejmech.2016.07.048. [PubMed] [CrossRef] [Google Scholar]323. Liu G.-N., Luo R.-H., Zhou Y., Zhang X.-J., Li J., Yang L.-M., Zheng Y.-T., Liu H. Synthesis and Anti-HIV-1 Activity Evaluation for Novel 3a,6a-Dihydro-1H-pyrrolo[3,4-c]pyrazole-4,6-dione Derivatives. Molecules. 2016;21:1198. doi: 10.3390/molecules21091198. [PMC free article] [PubMed] [CrossRef] [Google Scholar]324. Johns B.A., Gudmundsson K.S., Allen S.H. Pyrazolo[1,5-a]pyridine antiherpetics: Effects of the C3 substituent on antiviral activity. Bioorg. Med. Chem. Lett. 2007;17:2858–2862. doi: 10.1016/j.bmcl.2007.02.058.
[PubMed] [CrossRef] [Google Scholar]325. Chimenti F., Fioravanti R., Bolasco A., Manna F., Chimenti P., Secci D., Befani O., Turini P., Ortuso F., Alcaro S. Monoamine Oxidase Isoform-Dependent Tautomeric Influence in the Recognition of 3,5-Diaryl Pyrazole Inhibitors.
J. Med. Chem. 2007;50:425–428. doi: 10.1021/jm060868l. [PubMed] [CrossRef] [Google Scholar]326. Kuduk S.D., Di Marco C.N., Cofre V., Pitts D.R., Ray W.J., Ma L., Wittmann M., Veng L., Seager M.A., Koeplinger K. N-Heterocyclic derived M 1 positive allosteric modulators. Bioorg. Med. Chem. Lett. 2010;20:1334–1337.
doi: 10.1016/j.bmcl.2010.01.013. [PubMed] [CrossRef] [Google Scholar]327. Malamas M.S., Erdei J., Gunawan I., Barnes K., Hui Y., Johnson M., Robichaud A., Zhou P., Yan Y., Solvibile W. New pyrazolyl and thienyl aminohydantoins as potent BACE1 inhibitors: Exploring the S2′ region. Bioorg. Med. Chem. Lett. 2011;21:5164–5170.
doi: 10.1016/j.bmcl.2011.07.057. [PubMed] [CrossRef] [Google Scholar]328. Probst G., Aubele D.L., Bowers S., Dressen D., Garofalo A.W., Hom R.K., Konradi A.W., Marugg J.L., Mattson M.N., Neitzel M.L. Discovery of (R)-4-Cyclopropyl-7,8-difluoro-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-1H-pyrazolo[4,3-c]quinoline (ELND006) and (R)-4-Cyclopropyl-8-fluoro-5-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)-4,5-dihydro-2H-pyrazolo[4,3-c]quinoline (ELND007): Metabolically Stable γ-Secretase Inhibitors that Selectively Inhibit the Production of Amyloid-β over Notch. J. Med. Chem. 2013;56:5261–5274. doi: 10.1021/jm301741t. [PubMed] [CrossRef] [Google Scholar]329. Zou Y., Xu L., Chen W., Zhu Y., Chen T., Fu Y., Li L., Ma L., Xiong B., Wang X. Discovery of pyrazole as C-terminus of selective BACE1 inhibitors. Eur. J. Med. Chem. 2013;68:270–283.
doi: 10.1016/j.ejmech.2013.06.027. [PubMed] [CrossRef] [Google Scholar]330. Han Y.T., Kim K., Choi G.-I., An H., Son D., Kim H., Ha H.-J., Son J.-H., Chung S.-J., Park H.-J. Pyrazole-5-carboxamides, novel inhibitors of receptor for advanced glycation end products (RAGE) Eur. J. Med. Chem. 2014;79:128–142. doi: 10.1016/j.ejmech.2014.03.072.
[PubMed] [CrossRef] [Google Scholar]331. Silva D., Chioua M., Samadi A., Carreiras M.C., Jimeno M.-L., Mendes E., de los Ríos C., Romero A., Villarroya M., López M.G. Synthesis and pharmacological assessment of diversely substituted pyrazolo[3,4-b]quinoline, and benzo[b]pyrazolo[4,3-g][1,8]naphthyridine derivatives. Eur.
J. Med. Chem.
2011;46:4676–4681. doi: 10.1016/j.ejmech.2011.05.068. [PubMed] [CrossRef] [Google Scholar]332. Khoobi M., Ghanoni F., Nadri H., Moradi A., Hamedani M.P., Moghadam F.H., Emami S., Vosooghi M., Zadmard R., Foroumadi A. New tetracyclic tacrine analogs containing pyrano[2,3-c]pyrazole: Efficient synthesis, biological assessment and docking simulation study. Eur. J. Med. Chem. 2015;89:296–303. doi: 10.1016/j.ejmech.2014.10.049. [PubMed] [CrossRef] [Google Scholar]333. Zanaletti R., Bettinetti L., Castaldo C., Ceccarelli I., Cocconcelli G., Comery T.A., Dunlop J., Genesio E., Ghiron C., Haydar S.N. N-[5-(5-Fluoropyridin-3-yl)-1H-pyrazol-3-yl]-4-piperidin-1-ylbutyramide (SEN78702, WYE-308775): A Medicinal Chemistry Effort toward an α7 Nicotinic Acetylcholine Receptor Agonist Preclinical Candidate. J. Med. Chem. 2012;55:10277–10281. doi: 10.1021/jm3013568. [PubMed] [CrossRef] [Google Scholar]334. Zanaletti R., Bettinetti L., Castaldo C., Cocconcelli G., Comery T., Dunlop J., Gaviraghi G., Ghiron C., Haydar S.N., Jow F. Discovery of a novel alpha-7 nicotinic acetylcholine receptor agonist series and characterization of the potent, selective, and orally efficacious agonist 5-(4-acetyl[1,4]diazepan-1-yl)pentanoic acid[5-(4-methoxyphenyl)-1H-pyrazol-3-yl] amide (SEN15924, WAY-361789) J.
Med.
Chem. 2012;55:4806–4823. doi: 10.1021/jm300247y. [PubMed] [CrossRef] [Google Scholar]335. Nencini A., Castaldo C., Comery T.A., Dunlop J., Genesio E., Ghiron C., Haydar S., Maccari L., Micco I., Turlizzi E., et al. Design and synthesis of a hybrid series of potent and selective agonists of α7 nicotinic acetylcholine receptor. Eur. J. Med. Chem. 2014;78:401–418. doi: 10.1016/j.ejmech.2014.03.031. [PubMed] [CrossRef] [Google Scholar]336. Ernst G., Frietze W., Simpson T. Novel Pyrazole Derivatives and Their Use as Modulators of Nicotinic Acetylcholine Receptors. [(accessed on 2 October 2017)];Google Patents. 2008 Available online: . Thuring J.W.J.F., MacDonald G.J., Zhuang W. Trisubstituted Pyrazoles as Acetylcholine Receptor Modulators. [(accessed on 2 October 2017)];Google Patents. 2014 Available online: . Cottineau B., Toto P., Marot C., Pipaud A., Chenault J. Synthesis and hypoglycemic evaluation of substituted pyrazole-4-carboxylic acids. Bioorg. Med.
Chem. Lett. 2002;12:2105–2108. doi: 10.1016/S0960-894X(02)00380-3. [PubMed] [CrossRef] [Google Scholar]339. Sharon A., Pratap R., Tiwari P., Srivastava A., Maulik P.R., Ram V.J. Synthesis and in vivo antihyperglycemic activity of 5-(1H-pyrazol-3-yl)methyl-1H-tetrazoles. Bioorg. Med. Chem. Lett. 2005;15:2115–2117.
doi: 10.1016/j.bmcl.2005.02.060. [PubMed] [CrossRef] [Google Scholar]340. Humphries P.S., Lafontaine J.A., Agree C.S., Alexander D., Chen P., Do Q.-Q.T., Li L.Y., Lunney E.A., Rajapakse R.J., Siegel K. Synthesis and SAR of 4-substituted-2-aminopyrimidines as novel c-Jun N-terminal kinase (JNK) inhibitors. Bioorg. Med. Chem. Lett. 2009;19:2099–2102. doi: 10.1016/j.bmcl.2009.03.023. [PubMed] [CrossRef] [Google Scholar]341. Brigance R.P., Meng W., Fura A., Harrity T., Wang A., Zahler R., Kirby M.S., Hamann L.G. Synthesis and SAR of azolopyrimidines as potent and selective dipeptidyl peptidase-4 (DPP4) inhibitors for type 2 diabetes. Bioorg. Med. Chem. Lett. 2010;20:4395–4398.
doi: 10.1016/j.bmcl.2010.06.063. [PubMed] [CrossRef] [Google Scholar]342. Choi J., Park Y., Lee H.S., Yang Y., Yoon S. 1,3-Diphenyl-1H-pyrazole derivatives as a new series of potent PPARγ partial agonists. Bioorg. Med. Chem. 2010;18:8315–8323. doi: 10.1016/j.bmc.2010.09.068. [PubMed] [CrossRef] [Google Scholar]343. Shen D.-M., Brady E.J., Candelore M.R., Dallas-Yang Q., Ding V.D.H., Feeney W.P., Jiang G., McCann M.E., Mock S., Qureshi S.A., et al. Discovery of novel, potent, selective, and orally active human glucagon receptor antagonists containing a pyrazole core. Bioorg.
Med. Chem. Lett. 2011;21:76–81. doi: 10.1016/j.bmcl.2010.11.074. [PubMed] [CrossRef] [Google Scholar]344. Fushimi N., Fujikura H., Shiohara H., Teranishi H., Shimizu K., Yonekubo S., Ohno K., Miyagi T., Itoh F., Shibazaki T. Structure-activity relationship studies of 4-benzyl-1H-pyrazol-3-ylβ-d-glucopyranoside derivatives as potent and selective sodium glucose co-transporter 1 (SGLT1) inhibitors with therapeutic activity on postprandial hyperglycemia. Bioorg. Med. Chem. 2012;20:6598–6612. doi: 10.1016/j.bmc.2012.09.037. [PubMed] [CrossRef] [Google Scholar]345. Rikimaru K., Wakabayashi T., Abe H., Imoto H., Maekawa T., Ujikawa O., Murase K., Matsuo T., Matsumoto M., Nomura C. A new class of non-thiazolidinedione, non-carboxylic-acid-based highly selective peroxisome proliferator-activated receptor (PPAR) γ agonists: Design and synthesis of benzylpyrazole acylsulfonamides. Bioorg. Med. Chem. 2012;20:714–733. doi: 10.1016/j.bmc.2011.12.008. [PubMed] [CrossRef] [Google Scholar]346. Xiong Y., Guo J., Candelore M.R., Liang R., Miller C., Dallas-Yang Q., Jiang G., McCann P.E., Qureshi S.A., Tong X. Discovery of a Novel Glucagon Receptor Antagonist N-[(4-{(1S)-1-[3-(3,5-Dichlorophenyl)-5-(6-methoxynaphthalen-2-yl)-1H-pyrazol-1-yl]ethyl}phenyl)carbonyl]-β-alanine (MK-0893) for the Treatment of Type II Diabetes. J. Med. Chem. 2012;55:6137–6148.
doi: 10.1021/jm300579z. [PubMed] [CrossRef] [Google Scholar]347. Yoshida T., Akahoshi F., Sakashita H., Kitajima H., Nakamura M., Sonda S., Takeuchi M., Tanaka Y., Ueda N., Sekiguchi S.
Discovery and preclinical profile of teneligliptin (3-[(2S,4S)-4-[4-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazin-1-yl]pyrrolidin-2-ylcarbonyl]thiazolidine): A highly potent, selective, long-lasting and orally active dipeptidyl peptidase IV inhibitor for the treatment of type 2 diabetes. Bioorg. Med. Chem. 2012;20:5705–5719. doi: 10.1016/j.bmc.2012.08.012. [PubMed] [CrossRef] [Google Scholar]348. Futatsugi K., Mascitti V., Guimarães C.R., Morishita N., Cai C., DeNinno M.P., Gao H., Hamilton M.D., Hank R., Harris A.R. From partial to full agonism: Identification of a novel 2,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole as a full agonist of the human GPR119 receptor. Bioorg. Med.
Chem. Lett. 2013;23:194–197. doi: 10.1016/j.bmcl.2012.10.119. [PubMed] [CrossRef] [Google Scholar]349. Griffith D.A., Dow R.L., Huard K., Edmonds D.J., Bagley S.W., Polivkova J., Zeng D., Garcia-Irizarry C.N., Southers J.A., Esler W. Spirolactam-based acetyl-CoA carboxylase inhibitors: Toward improved metabolic stability of a chromanone lead structure. J. Med. Chem.
2013;56:7110–7119. doi: 10.1021/jm401033t. [PubMed] [CrossRef] [Google Scholar]350. Hernández-Vázquez E., Aguayo-Ortiz R., Ramírez-Espinosa J.J., Estrada-Soto S., Hernández-Luis F. Synthesis, hypoglycemic activity and molecular modeling studies of pyrazole-3-carbohydrazides designed by a CoMFA model. Eur. J. Med. Chem. 2013;69:10–21. doi: 10.1016/j.ejmech.2013.07.054. [PubMed] [CrossRef] [Google Scholar]351. Toda N., Hao X., Ogawa Y., Oda K., Yu M., Fu Z., Chen Y., Kim Y., Lizarzaburu M., Lively S.
Potent and orally bioavailable GPR142 agonists as novel insulin secretagogues for the treatment of type 2 diabetes. ACS Med. Chem. Lett. 2013;4:790–794. doi: 10.1021/ml400186z. [PMC free article] [PubMed] [CrossRef] [Google Scholar]352. Yu M., Lizarzaburu M., Motani A., Fu Z., Du X., Liu J., Jiao X., Lai S., Fan P., Fu A. Aminopyrazole–Phenylalanine Based GPR142 Agonists: Discovery of Tool Compound and in Vivo Efficacy Studies. ACS Med. Chem. Lett. 2013;4:829–834. doi: 10.1021/ml4000854. [PMC free article] [PubMed] [CrossRef] [Google Scholar]353. Bhosle M.R., Mali J.R., Pal S., Srivastava A.K., Mane R.A. Synthesis and antihyperglycemic evaluation of new 2-hydrazolyl-4-thiazolidinone-5-carboxylic acids having pyrazolyl pharmacophores. Bioorg. Med. Chem. Lett. 2014;24:2651–2654. doi: 10.1016/j.bmcl.2014.04.064. [PubMed] [CrossRef] [Google Scholar]354.
López-Viseras M.E., Fernández B., Hilfiker S., González C.S., González J.L., Calahorro A.J., Colacio E., Rodríguez-Diéguez A. In vivo potential antidiabetic activity of a novel zinc coordination compound based on 3-carboxy-pyrazole. J. Inorg. Biochem. 2014;131:64–67. doi: 10.1016/j.jinorgbio.2013.10.019. [PubMed] [CrossRef] [Google Scholar]355. Kenchappa R., Bodke Y.D., Chandrashekar A., Sindhe M.A., Peethambar S. Synthesis of coumarin derivatives containing pyrazole and indenone rings as potent antioxidant and antihyperglycemic agents. Arab. J. Chem. 2017;10:S3895–S3906. doi: 10.1016/j.arabjc.2014.05.029. [CrossRef] [Google Scholar]356. Doddaramappa S.D., Lokanatha Rai K.M., Srikantamurthy N., Chethan J. Novel 5-functionalized-pyrazoles: Synthesis, characterization and pharmacological screening. Bioorg. Med. Chem. Lett. 2015;25:3671–3675. doi: 10.1016/j.bmcl.2015.06.050. [PubMed] [CrossRef] [Google Scholar]357. Hernández-Vázquez E., Salgado-Barrera S., Ramírez-Espinosa J.J., Estrada-Soto S., Hernández-Luis F. Synthesis and molecular docking of N′-arylidene-5-(4-chlorophenyl)-1-(3,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carbohydrazides as novel hypoglycemic and antioxidant dual agents. Bioorg. Med. Chem. 2016;24:2298–2306. doi: 10.1016/j.bmc.2016.04.007. [PubMed] [CrossRef] [Google Scholar]358. Kashtoh H., Muhammad M.T., Khan J.J.A., Rasheed S., Khan A., Perveen S., Javaid K., Atia tul W., Khan K.M., Choudhary M.I. Dihydropyrano[2,3-c]pyrazole: Novel in vitro inhibitors of yeast α-glucosidase. Bioorg. Chem. 2016;65:61–72. doi: 10.1016/j.bioorg.2016.01.008. [PubMed] [CrossRef] [Google Scholar]359. Chaudhry F., Naureen S., Huma R., Shaukat A., Al-Rashida M., Asif N., Ashraf M., Munawar M.A., Khan M.A. In search of new α-glucosidase inhibitors: Imidazolylpyrazole derivatives. Bioorg. Chem. 2017;71:102–109. doi: 10.1016/j.bioorg.2017.01.017.
[PubMed] [CrossRef] [Google Scholar]360. Hernández-Vázquez E., Ocampo-Montalban H., Cerón-Romero L., Cruz M., Gómez-Zamudio J., Hiriart-Valencia G., Villalobos-Molina R., Flores-Flores A., Estrada-Soto S. Antidiabetic, antidyslipidemic and toxicity profile of ENV-2: A potent pyrazole derivative against diabetes and related diseases. Eur. J. Pharmacol. 2017;803:159–166. doi: 10.1016/j.ejphar.2017.03.036.
[PubMed] [CrossRef] [Google Scholar]361. De Mello H., Echevarria A., Bernardino A.M., Canto-Cavalheiro M., Leon L.L. Antileishmanial pyrazolopyridine derivatives: Synthesis and structure-activity relationship analysis. J.
Med. Chem. 2004;47:5427–5432. doi: 10.1021/jm0401006. [PubMed] [CrossRef] [Google Scholar]362. Bernardino A.M.R., Gomes A.O., Charret K.S., Freitas A.C.C., Machado G.M.C., Canto-Cavalheiro M.M., Leon L.L., Amaral V.F. Synthesis and leishmanicidal activities of 1-(4-X-phenyl)-N′-[(4-Y-phenyl)methylene]-1H-pyrazole-4-carbohydrazides. Eur. J. Med. Chem. 2006;41:80–87. doi: 10.1016/j.ejmech.2005.10.007. [PubMed] [CrossRef] [Google Scholar]363. Dardari Z., Lemrani M., Sebban A., Bahloul A., Hassar M., Kitane S., Berrada M., Boudouma M. Antileishmanial and Antibacterial Activity of a New Pyrazole Derivative Designated 4-[2-(1-(Ethylamino)-2-methyl-propyl) phenyl]-3-(4-methyphenyl)-1-phenylpyrazole. Arch. Pharm. 2006;339:291–298. doi: 10.1002/ardp.200500266. [PubMed] [CrossRef] [Google Scholar]364. Dos Santos M.S., Gomes A.O., Bernardino A.M., Souza M.C.D., Khan M.A., Brito M.A.D., Castro H.C., Abreu P.A., Rodrigues C.R., de Léo R.M. Synthesis and antileishmanial activity of new 1-aryl-1H-pyrazole-4-carboximidamides derivatives. J. Braz. Chem. Soc. 2011;22:352–358. doi: 10.1590/S0103-50532011000200022. [CrossRef] [Google Scholar]365. Dos Santos M.S., Oliveira M.L., Bernardino A.M., de Léo R.M., Amaral V.F., de Carvalho F.T., Leon L.L., Canto-Cavalheiro M.M. Synthesis and antileishmanial evaluation of 1-aryl-4-(4,5-dihydro-1H-imidazol-2-yl)-1H-pyrazole derivatives. Bioorg. Med. Chem. Lett. 2011;21:7451–7454. doi: 10.1016/j.bmcl.2011.09.134. [PubMed] [CrossRef] [Google Scholar]366.
Jacomini A.P., Silva M.J.V., Silva R.G.M., Gonçalves D.S., Volpato H., Basso E.A., Paula F.R., Nakamura C.V., Sarragiotto M.H., Rosa F.A. Synthesis and evaluation against Leishmania amazonensis of novel pyrazolo[3,4-d]pyridazinone-N-acylhydrazone-(bi)thiophene hybrids. Eur. J.
Med. Chem. 2016;124:340–349. doi: 10.1016/j.ejmech.2016.08.048. [PubMed] [CrossRef] [Google Scholar]367. Bekhit A.A., Hassan A.M.M., Abd El Razik H.A., El-Miligy M.M.M., El-Agroudy E.J., Bekhit A.E.-D.A. New heterocyclic hybrids of pyrazole and its bioisosteres: Design, synthesis and biological evaluation as dual acting antimalarial-antileishmanial agents. Eur. J.

Med. Chem. 2015;94:30–44. doi: 10.1016/j.ejmech.2015.02.038. [PubMed] [CrossRef] [Google Scholar]368. Mowbray C.E., Braillard S., Speed W., Glossop P.A., Whitlock G.A., Gibson K.R., Mills J.E.J., Brown A.D., Gardner J.M.F., Cao Y., et al. Novel Amino-pyrazole Ureas with Potent In Vitro and In Vivo Antileishmanial Activity. J.
Med. Chem. 2015;58:9615–9624. doi: 10.1021/acs.jmedchem.5b01456. [PubMed] [CrossRef] [Google Scholar]369. Marra R., Bernardino A., Proux T., Charret K., Lira M.-L., Castro H., Souza A., Oliveira C., Borges J., Rodrigues C., et al. 4-(1H-Pyrazol-1-yl)Benzenesulfonamide Derivatives: Identifying New Active Antileishmanial Structures for Use against a Neglected Disease.
Molecules. 2012;17:12961–12973. doi: 10.3390/molecules171112961. [PMC free article] [PubMed] [CrossRef] [Google Scholar]370. Bekhit A.A., Haimanot T., Hymete A. Evaluation of some 1H-pyrazole derivatives as a dual acting antimalarial and anti-leishmanial agents. Pak. J. Pharm.
Sci. 2014;27:1767–1773. [PubMed] [Google Scholar]371. Figarella K., Marsiccobetre S., Galindo-Castro I., Urdaneta N., Herrera J., Canudas N., Galarraga E. Antileishmanial and antitrypanosomal activity of synthesized hydrazones, pyrazoles, pyrazolo [1,5-a]-pyrimidines and pyrazolo[3,4-b]-pyridine. Curr. Bioact. Compd. 2017;13
doi: 10.2174/1573407213666170405121810. [CrossRef] [Google Scholar]372. Tuha A., Bekhit A.A., Seid Y. Screening of some pyrazole derivatives as promising antileishmanial agent. Afr. J. Pharm. Pharmacol. 2017;11:32–37. doi: 10.5897/AJPP2016.4401. [CrossRef] [Google Scholar]373. Reviriego F., Olmo F., Navarro P., Marín C., Ramírez-Macías I., García-España E., Albelda M.T., Gutiérrez-Sánchez R., Sánchez-Moreno M., Arán V.J. Simple dialkyl pyrazole-3,5-dicarboxylates show in vitro and in vivo activity against disease-causing trypanosomatids. Parasitology. 2017;144:1133–1143. doi: 10.1017/S0031182017000415. [PubMed] [CrossRef] [Google Scholar]374. Domínguez J.N., Charris J.E., Caparelli M., Riggione F. Synthesis and antimalarial activity of substituted pyrazole derivatives. Arzneimittel-Forschung. 2002;52:482–488. doi: 10.1055/s-0031-1299918. [PubMed] [CrossRef] [Google Scholar]375. Mishra S., Karmodiya K., Surolia N., Surolia A. Synthesis and exploration of novel curcumin analogues as anti-malarial agents. Bioorg. Med. Chem. 2008;16:2894–2902. doi: 10.1016/j.bmc.2007.12.054. [PubMed] [CrossRef] [Google Scholar]376.
González Cabrera D., Douelle F., Feng T.-S., Nchinda A.T., Younis Y., White K.L., Wu Q., Ryan E., Burrows J.N., Waterson D. Novel orally active antimalarial thiazoles. J. Med. Chem. 2011;54:7713–7719. doi: 10.1021/jm201108k. [PubMed] [CrossRef] [Google Scholar]377. Quirante J., Ruiz D., Gonzalez A., López C., Cascante M., Cortés R., Messeguer R., Calvis C., Baldomà L., Pascual A. Platinum (II) and palladium (II) complexes with (N,N′) and (C,N,N′)–ligands derived from pyrazole as anticancer and antimalarial agents: Synthesis, characterization and in vitro activities. J. Inorg. Biochem.
2011;105:1720–1728.
doi: 10.1016/j.jinorgbio.2011.09.021. [PubMed] [CrossRef] [Google Scholar]378.
Large J.M., Osborne S.A., Smiljanic-Hurley E., Ansell K.H., Jones H.M., Taylor D.L., Clough B., Green J.L., Holder A.A. Imidazopyridazines as potent inhibitors of Plasmodium falciparum calcium-dependent protein kinase 1 (PfCDPK1): Preparation and evaluation of pyrazole linked analogues. Bioorg. Med. Chem. Lett. 2013;23:6019–6024.
doi: 10.1016/j.bmcl.2013.08.010. [PMC free article] [PubMed] [CrossRef] [Google Scholar]379. Balaji S.N., Ahsan M.J., Jadav S.S., Trivedi V. Molecular modelling, synthesis, and antimalarial potentials of curcumin analogues containing heterocyclic ring. Arab. J. Chem. 2015 doi: 10.1016/j.arabjc.2015.04.011.
[CrossRef] [Google Scholar]380. Niswender C.M., Lebois E.P., Luo Q., Kim K., Muchalski H., Yin H., Conn P.J., Lindsley C.W. Positive allosteric modulators of the metabotropic glutamate receptor subtype 4 (mGluR4): Part I. Discovery of pyrazolo[3,4-d]pyrimidines as novel mGluR4 positive allosteric modulators. Bioorg. Med. Chem.
Lett. 2008;18:5626–5630. doi: 10.1016/j.bmcl.2008.08.087. [PMC free article] [PubMed] [CrossRef] [Google Scholar]381. Chimenti F., Carradori S., Secci D., Bolasco A., Bizzarri B., Chimenti P., Granese A., Yanez M., Orallo F. Synthesis and inhibitory activity against human monoamine oxidase of N1-thiocarbamoyl-3,5-di(hetero)aryl-4,5-dihydro-(1H)-pyrazole derivatives. Eur. J. Med. Chem. 2010;45:800–804. doi: 10.1016/j.ejmech.2009.11.003. [PubMed] [CrossRef] [Google Scholar]382. Maher P., Akaishi T., Schubert D., Abe K. A pyrazole derivative of curcumin enhances memory. Neurobiol. Aging. 2010;31:706–709. doi: 10.1016/j.neurobiolaging.2008.05.020. [PubMed] [CrossRef] [Google Scholar]383. Chan B.K., Estrada A.A., Chen H., Atherall J., Baker-Glenn C., Beresford A., Burdick D.J., Chambers M., Dominguez S.L., Drummond J. Discovery of a highly selective, brain-penetrant aminopyrazole LRRK2 inhibitor. ACS Med. Chem. Lett. 2012;4:85–90. doi: 10.1021/ml3003007. [PMC free article] [PubMed] [CrossRef] [Google Scholar]384. Jimenez H.N., Liu K.G., Hong S.-P., Reitman M.S., Uberti M.A., Bacolod M.D., Cajina M., Nattini M., Sabio M., Doller D. 4-(1-Phenyl-1H-pyrazol-4-yl) quinolines as novel, selective and brain penetrant metabotropic glutamate receptor 4 positive allosteric modulators. Bioorg. Med. Chem. Lett. 2012;22:3235–3239.
doi: 10.1016/j.bmcl.2012.03.032.
[PubMed] [CrossRef] [Google Scholar]385. Dore A., Asproni B., Scampuddu A., Pinna G.A., Christoffersen C.T., Langgård M., Kehler J. Synthesis and SAR study of novel tricyclic pyrazoles as potent phosphodiesterase 10A inhibitors. Eur. J. Med. Chem. 2014;84:181–193. doi: 10.1016/j.ejmech.2014.07.020. [PubMed] [CrossRef] [Google Scholar]386. Estrada A.A., Chan B.K., Baker-Glenn C., Beresford A., Burdick D.J., Chambers M., Chen H., Dominguez S.L., Dotson J., Drummond J. Discovery of highly potent, selective, and brain-penetrant aminopyrazole leucine-rich repeat kinase 2 (LRRK2) small molecule inhibitors. J. Med. Chem. 2014;57:921–936. doi: 10.1021/jm401654j. [PubMed] [CrossRef] [Google Scholar]387. Fujinaga M., Yamasaki T., Nengaki N., Ogawa M., Kumata K., Shimoda Y., Yui J., Xie L., Zhang Y., Kawamura K., et al. Radiosynthesis and evaluation of 5-methyl-N-(4-[11C]methylpyrimidin-2-yl)-4-(1H-pyrazol-4-yl)thiazol-2-amine ([11C]ADX88178) as a novel radioligand for imaging of metabotropic glutamate receptor subtype 4 (mGluR4) Bioorg. Med.
Chem. Lett. 2016;26:370–374. doi: 10.1016/j.bmcl.2015.12.008. [PubMed] [CrossRef] [Google Scholar]388. Kim M., Sim C., Shin D., Suh E., Cho K. Residual and sublethal effects of fenpyroximate and pyridaben on the instantaneous rate of increase of Tetranychus urticae. Crop Prot. 2006;25:542–548. doi: 10.1016/j.cropro.2005.08.010. [CrossRef] [Google Scholar]389. Selby T.P., Lahm G.P., Stevenson T.M., Hughes K.A., Cordova D., Annan I.B. Discovery of cyantraniliprole, a potent and selective anthranilic diamide ryanodine receptor activator with cross-spectrum insecticidal activity. Bioorg. Med. Chem. Lett.
2013;23:6341–6345. doi: 10.1016/j.bmcl.2013.09.076. [PubMed] [CrossRef] [Google Scholar]390. Yu H., Xu M., Cheng Y., Wu H., Luo Y., Li B. Synthesis and acaricidal activity of cyenopyrafen and its geometric isomer. Arkivoc. 2012;6:26–34. doi: 10.3998/ark.5550190.0013.603. [CrossRef] [Google Scholar]391. Marcic D. Sublethal effects of tebufenpyrad on the eggs and immatures of two-spotted spider mite, Tetranychus urticae. Exp. Appl.
Acarol. 2005;36:177–185. doi: 10.1007/s10493-005-3579-2.
[PubMed] [CrossRef] [Google Scholar]392.
Nonaka N. Tolfenpyrad—A New Insecticide with Wide Spectrum and Unique Action. Agrochem. Jpn. 2003;83:17–19. [Google Scholar]393. Finkelstein B.L., Strock C.J. Synthesis and Insecticidal Activity of Novel Pyrazole Methanesulfonates. Pest. Sci. 1997;50:324–328. doi: 10.1002/(SICI)1096-9063(199708)50:4<324::AID-PS596>3.0.CO;2-D.
[CrossRef] [Google Scholar]394. Mao M., Li Y., Liu Q., Zhou Y., Zhang X., Xiong L. Synthesis and insecticidal evaluation of novel N-pyridylpyrazolecarboxamides containing cyano substituent in the ortho-position. Bioorg. Med. Chem.
Lett. 2013;23:42–46.
doi: 10.1016/j.bmcl.2012.11.045. [PubMed] [CrossRef] [Google Scholar]395. Wu J., Song B.A., Hu D.Y., Yue M., Yang S. Design, synthesis and insecticidal activities of novel pyrazole amides containing hydrazone substructures. Pest. Manag.
Sci. 2012;68:801–810. doi: 10.1002/ps.2329. [PubMed] [CrossRef] [Google Scholar]396. Dai H., Xiao Y.-S., Li Z., Xu X.-Y., Qian X.-H. The thiazoylmethoxy modification on pyrazole oximes: Synthesis and insecticidal biological evaluation beyond acaricidal activity. Chin. Chem.
Lett. 2014;25:1014–1016. doi: 10.1016/j.cclet.2014.06.011.
[CrossRef] [Google Scholar]397. Song H., Liu Y., Xiong L., Li Y., Yang N., Wang Q. Design, synthesis, and insecticidal activity of novel pyrazole derivatives containing α-hydroxymethyl-N-benzyl carboxamide, α-chloromethyl-N-benzyl carboxamide, and 4,5-dihydrooxazole moieties. J. Agric. Food. Chem. 2012;60:1470–1479.
doi: 10.1021/jf204778v. [PubMed] [CrossRef] [Google Scholar]398.
Fu C., Pei J., Ning Y., Liu M., Shan P., Liu J. Synthesis and insecticidal activities of novel pyrazole oxime ether derivatives with different substituted pyridyl rings. Pest. Manag. Sci. 2014;70:1207–1214. doi: 10.1002/ps.3672. [PubMed] [CrossRef] [Google Scholar]399.
Ma H.-J., Li Y.-H., Zhao Q.-F., Zhang T., Xie R.-L., Mei X.-D. Synthesis and herbicidal activity of novel N-(2,2,2)-trifluoroethylpyrazole derivatives. J. Agric. Food Chem. 2010;58:4356–4360. doi: 10.1021/jf9042166. [PubMed] [CrossRef] [Google Scholar]400. Dai H., Chen J., Li H., Dai B., He H., Fang Y.
Synthesis and Bioactivities of Novel Pyrazole Oxime Derivatives Containing a 5-Trifluoromethylpyridyl Moiety. Molecules. 2016;21:276.
doi: 10.3390/molecules21030276. [PMC free article] [PubMed] [CrossRef] [Google Scholar]401. Li M., Liu C.-L., Yang J.-C., Zhang J.-B., Li Z.-N., Zhang H. Synthesis and biological activity of new (E)-α-(methoxyimino)benzeneacetate derivatives containing a substituted pyrazole ring. J.
Agric. Food Chem. 2009;58:2664–2667. doi: 10.1021/jf9026348. [PubMed] [CrossRef] [Google Scholar]402. Fustero S., Román R., Sanz-Cervera J.F., Simón-Fuentes A., Bueno J., Villanova S. Synthesis of new fluorinated tebufenpyrad analogs with acaricidal activity through regioselective pyrazole formation. J. Org. Chem. 2008;73:8545–8552.
doi: 10.1021/jo801729p. [PubMed] [CrossRef] [Google Scholar]403.
Vicentini C.B., Mares D., Tartari A., Manfrini M., Forlani G. Synthesis of pyrazole derivatives and their evaluation as photosynthetic electron transport inhibitors.
J.
Agric. Food Chem. 2004;52:1898–1906. doi: 10.1021/jf035115b. [PubMed] [CrossRef] [Google Scholar]404. Zhao Q., Li Y., Xiong L., Wang Q. Design, synthesis and insecticidal activity of novel phenylpyrazoles containing a 2,2,2-trichloro-1-alkoxyethyl moiety. J. Agric. Food Chem. 2010;58:4992–4998. doi: 10.1021/jf1001793. [PubMed] [CrossRef] [Google Scholar] 1Universitary Center of Anápolis, UniEvangélica, Anápolis, Brazil2Laboratory of Pharmacology of Natural and Synthetic Products, Institute of Biological Sciences, Federal University of Goiás, Goiânia, Brazil3Center for Neuroscience and Cardiovascular Research, Department of Physiology, Institute of Biological Sciences, Federal University of Goiás, Goiânia, Brazil4Institute of Science, Technology and Quality (ICTQ), Anápolis, Brazil5Systems Neurobiology Laboratory, Department of Physiology, Institute of Biological Sciences, Federal University of Goiás, Goiânia, Brazil6Theoretical and Structural Chemistry Group, Universidade Estadual de Goiás, Anápolis, Brazil7Goiás State University, Itumbiara, Brazil8Laboratory of Electrophysiology and Cardiovascular Physiology, Department of Physiology, Institute of Biomedical Science, Federal University of Uberlândia, Uberlândia, Brazil9Laboratory of Medicinal Pharmaceutical Chemistry, Faculty of Pharmacy, Federal University of Goiás, Goiânia, BrazilLow quality of life and life-threatening conditions often demand pharmacological screening of lead compounds. A spectrum of pharmacological activities has been attributed to pyrazole analogs. The substitution, replacement, or removal of functional groups on a pyrazole ring appears consistent with diverse molecular interactions, efficacy, and potency of these analogs. This mini-review explores cytotoxic, cytoprotective, antinociceptive, anti-inflammatory, and antidepressant activities of some pyrazole analogs to advance structure-related pharmacological profiles and rational design of new analogs. Numerous interactions of these derivatives at their targets could impact future research considerations and prospects while offering opportunities for optimizing therapeutic activity with fewer adverse effects.Medicinal chemistry is engaged in the research area to ameliorate new derivatives (Zhao, 2007).

With wide application in medicine and industry (Al-Omar, 2010), the pyrazole ring is important in rational drug development. As a privileged structure present in different classes of drugs, the pyrazole moiety has inspired new classes of drug development (Faria et al., 2017; Patil, 2020; Yet, 2018). The pyrazole moiety is a nitrogen-containing heterocyclic core with diverse targets and effects (Figure 1) (Faisal et al., 2019; Ran et al., 2019; Taher et al., 2019; Badavath and Jayaprakash, 2020). The series of available pyrazole analogs could provide clues to structural activity relationship (SAR) and predict potential therapeutic or adverse effects.FIGURE 1. Effects evoked by pyrazole analogs in different cells target.The substitutions, additions, removal, or fusion of different functional groups in the pyrazole ring are key to the synthesis of lead compounds that are effective against emerging and complex diseases (Faisal et al., 2019; Aziz et al., 2020; Ramsay et al., 2018; Benek et al., 2020; He et al., 2016). Pharmacological characterization of these analogs will benefit from our comprehension of the functional group modifications on the central pyrazole ring (Figure 2). The standard drugs containing the pyrazole ring [pyrazofurin (anticancer), crizotinib (cytoprotective), celecoxib and lonazolac (anti-inflammatory), difenamizole (analgesic), rimonabant (anti-obesity), sildenafil (vasodilator), and fezolamide (antidepressant)] (Hill and Whelan, 1980; Kameyama et al., 1981; Clemett and Goa, 2000; Samat et al., 2008; Straube, 2012; Dopp et al., 2013; Mitou et al., 2015; Karrouchi et al., 2018) provide ample opportunity for continuous research and analysis of new analogs.FIGURE 2.

Functional groups that confer some distinctive interactions and activities on pyrazole analogs.This mini-review explores selected activities and structural modifications of some pyrazole analogs. The available data on the concentration of analogs required for 50% inhibition (IC50), equilibrium dissociation constant for the inhibitor (Ki), the dose that elicited 50% of the maximum possible effect (ED50), ulcerogenic index (UI), or selectivity index (SI) are provided to further comparative discussions on their affinity, efficacy, and potency. As the present review is limited to selected biological activities, the author's considerations, and future perspectives on some representative analogs (see Supplementary Table S1), additional references are listed for the aspects that are out of the present scope. All the chemical structures and figures were designed using either ChemDraw JS program or biorender.com.Selected ActivitiesCytotoxic and Cytoprotective ActivitiesThe cytotoxic effects of some pyrazole analogs against specific cell lines including human breast cancer cells (MDA-MB-231 and MCF-7) appear promising to the development of anticancer drugs (Kamel, 2015).

Compound 1 containing a distal pyrazole ring and sulphonyl moiety decreased the viability of MCF7 (IC50 = 39.70 μM). Unlike non-heterocyclic compound 4, the activities of caspase-3 and caspase-7 in MDA-MB-231 were gradually reduced by compounds 1–3. With the data showing the cleavage of caspase-8 and caspase-9 through caspase-3 and caspase-7 activation in the cascade of caspases (Toton et al., 2013), compound 4 is unlikely to elicit a specific effect. Since caspases play different roles in cellular survival, differentiation, and proliferation process, specific caspase inhibition by compounds 1–3 suggests a safety profile (Lehmann et al., 2017). Potent antiproliferative activity (IC50 = 0.26 μM) and mitogen-activated protein kinase inhibition (MEK, IC50 = 91 nM) have been attributed to methyl and ortho-fluorine groups on pyrazole carboxamide of compound 5. This result suggests suppression of abnormal signaling of the MEK-dependent pathways. In the docking assay, the contribution of the 1,3-diphenyl-1H-pyrazole to hydrophobic interactions (Val 82, Ala 95, Val 127, Met 143, Met 143, and Leu 197 of the ATP-binding pocket) and MEK inhibition (Lv et al., 2016) was considered significant. Recently, a thiazole moiety was attached to the pyrazole ring and assayed against different cancer cell lines (Masaret, 2021). Relatively high cytotoxic efficacy of compounds 6–8 (IC50 = 14.32, 11.17, and 10.21, respectively) against MCF-7 supports the antitumor role of the thiazole moiety (Masaret, 2021). However, the specificity of the cytotoxic potential and emerging resistance still need to be extensively evaluated.As some analogs are considered potent IC50 < 100 nM; mild IC50 > 10,000 nM cytotoxic or noncytotoxic on some cell lines, and others elicit cyto- or neuroprotection. The restoration of redox homeostasis or prevention of oxidative stress, inflammation, glycation, and vascular injury is key to neuroprotection (Hrelia et al., 2020). Chemically diverse pyrazole analogs have shown promising cellular or neuronal protections. The bulky dicyclohexylamide (9), smaller dimethylamide (10), and aminophenyl (11) (pyrazole analogs with sterically hindered substituents on amide) attenuated microglia-mediated neurotoxicity (IC50 = 10–50 μM) better than compound 12 (IC50 = 100 μM) with high susceptibility to electrophilic displacement (McKenzie et al., 2019). This compound contains an allyl group on an electron-deficient amide. Suppression of toxin-induced microglia overactivation offers a therapeutic opportunity capable of halting the progression of reactive oxygen species–induced neurodegenerative disease (Block et al., 2007). The electron-withdrawing substituents such as para-bromo on the aldehyde aromatic ring (13) elicited higher neuroprotective activity than the electron-donating substituent (Gameiro et al., 2017). This activity involves the inhibition of glycogen synthase kinase 3β (GSK3β; IC50 = 3.77 μM) and induction of nuclear factor (erythroid-derived 2)–like 2 (Nrf2; luciferase activity = 3–30 μM). As regulators of cellular responses, both GSK3β and Nrf2 are key neurodegenerative targets (Brandes and Gray, 2020; Toral-Rios et al., 2020).Analogs with the para-bromophenyl radical attached to the pyrazole ring (14, 15, and 16) target the metabolic enzymes (acetylcholinesterase—AChE, carbonic anhydrase—hCA, and α-glycosidase—α-GlyIs) that are relevant to neurodegenerative disorders. However, the number of phenyl substituents on the pyrazole ring seems to create a specific pattern of metabolic enzyme inhibition. Turkan et al. (2018) attributed potent AChE inhibition to compound 15 with triphenyl substitutions (IC50 = 66.37 nM), α-GlyIs inhibition to analogs with diphenyl substitutions (14 and 16; IC50 = 43.72 and 36.02 nM, respectively), and hCA I and II isoform inhibition (IC50 = 0.93 and 0.75 nM, respectively) to compound 9 with two bromophenyl substitutions.

Altogether, the inhibitory effects of these analogs on specific regulators of cellular processes could alter ATP production, functions of organelles, redox reactions, and proliferative, vascular, and inflammatory responses.Antinociceptive and Anti-inflammatory ActivitiesAs pain is a hallmark of tissue damage and inflammatory processes (Baral et al., 2019), pyrazole analogs with antinociceptive and anti-inflammatory activities are important to analgesic drug development.

The pyrazole compounds with fluorine at para (17), meta (18), and ortho (19) positions on the phenyl ring demonstrated an antinociceptive effect in the previous studies (de Oliveira et al., 2017; Florentino et al., 2019). This effect was associated with the activation of the opioid receptor and blockage of the acid-sensing ion channel subtype 1α (ASIC-1α). The para substitution improved the interaction with peripheral opioid receptors, while ortho substitution reduced the ASIC-1α channel's affinity. The antagonism of transient receptor potential vanilloid subtype 1 (TRPV-1) seems to be optimized by the 3-chlorophenyl and 3-chloro-4-fluorophenyl substitutions (20 and 21, respectively) at the N1 position of the pyrazole C-region. The opioid receptors ASIC-1α and TRPV-1 are important targets of nociceptive modulation. Higher antinociceptive efficacy was reported in compound 21 (ED50 = 57 mg/kg). Like indomethacin (24% of pain inhibition), compound 22 with chloro and trifluoromethyl groups on phenyl and benzofuran template, respectively, elicited a similar 24% of pain inhibition (El Shehry et al., 2019). According to Kenchappa and Bodke (2020), compound 23 (benzofuran pyrazole substituted with nitro and bromo groups) inhibited pain response (60%) better than compounds 24 and 25 with benzofuran carbaldehyde (35 and 50%, respectively). These results support the elevation of antinociceptive efficacy through the addition of electron-withdrawing groups. Meanwhile, different group substitutions on other positions of pyrazole rings could offer additional data on potency and efficacy. The 4-(arylchalcogenyl)-1H-pyrazole analog containing the selanyl or sulfenyl group (26 and 27) elicited a higher nociceptive threshold in formalin, glutamate, and acid-induced abdominal writhing than compound 28 without the organochalcogen group (Oliveira et al., 2020).

The modulation of oxidative and inflammatory pathways has been associated with pain inhibition (23%) by analogs with 2,3-di-tert-butylphenol (29) in Freund's complete adjuvant–induced mechanical hyperalgesia (Galvão et al., 2020). A longer carbon chain (30) and levulinic (31) analogs with 47 and 50% pain inhibition, respectively (Taher et al., 2019), suggests that the length of the aliphatic chain could elicit a subtle change in the antinociceptive effect. In respect of first-line analgesic drugs, the fusion of pyrimidine moiety to the pyrazole backbone (32) similarly increased thermal latency (160%) and reduced abdominal writhing (83%) as compared with tramadol (175%) and aspirin (78%), respectively (Khalifa et al., 2019).The addition of the adamantyl residue to 1,5-diaryl pyrazole (33) elicited a higher anti-inflammatory activity over the antinociceptive effect. The anti-inflammatory effect of pyrazole analogs could be assessed through edema formation (a cardinal sign of inflammation). Compound 33 induced a lower antiedematogenic effect than the reference drug celecoxib (39 and 82% of edema inhibition, respectively). Celecoxib exhibited higher potency of cyclooxygenase (COX)-2 inhibition than compound 33 (IC50 = 0.95 and 2.52 μM, respectively) (Abdelazeem et al., 2020). New azomethine compounds with an electron-withdrawing group like nitrogen (34) or chlorine (35) at the ortho position of phenyl ring with a satisfactory anti-inflammatory effect (ED50 = 0.86 and 0.92 mmol/kg, respectively) elicited weak COX-2 inhibition (IC50 = 38.12 and 32.11) as compared with celecoxib (ED50 = 8.03 mmol/kg; IC50 = 0.34) (Murahari et al., 2019). These results support the importance of electron-withdrawing groups toward the development of highly potent anti-inflammatory analogs. The thiohydantoin derivatives with pyrazole core and methoxy substituents (36–39) induced promising antiedematogenic activity (ED50 = 55–62 μmol/kg) as compared with celecoxib (ED50 = 78 μmol/kg). The methoxy moiety (the electron-donating group) of these analogs confers additional hydrogen bonding and interaction with COX-2 active sites (Lys68, Tyr108, Tyr341, Arg106, and Arg499). This attribute supports a higher range of binding energy among compounds 36–39 (16–20 kcal/mol) as compared with celecoxib (17 kcal/mol) with fewer hydrogen bonding (Ser516 and Tyr371) (Abdellatif et al., 2019). An additional evaluation revealed a better COX-2 inhibition with chloroacetamide (40) and acetamide morpholine (41) compounds (IC50 = 20 and 34 nM, respectively). In comparison with compound 40, the propionamide morpholine (42) analog improved the selectivity index (SI = 5 and 22, respectively). Compounds 40 and 42 significantly inhibited cytosolic (31 and 44%) and microsomal (81 and 74%) prostaglandin E2 synthase. The antiedematogenic activity of these analogs (46 and 44%) appears similar to the analog of celecoxib (42%).Molecular docking data portraying compound 42 as the most active analog (Hassan et al., 2019) provide clues to the role of the morpholine (heterocyclic nucleus) with electron-withdrawing substituents on the phenyl ring. Additional COX-2 interactions (Gln192 and Phe518) and improved anti-inflammatory effects seem to be related to this chemical modification. Meanwhile, the COX-2 selectivity index (SI = 417) and the anti-inflammatory effect (% edema inhibition = 87%) of compound 43 with amino and methanesulphonyl groups are very close to that of celecoxib (SI = 327; % edema inhibition = 83%). This finding suggests robust aminosulfonyl moiety interaction with Gln178, Arg499, Phe504, and Gln178 amino acid residues of COX-2 (Abdellatif et al., 2020). The growing interest in pyrazole analogs with dual COX/LOX (lipoxygenase) inhibition has widened the scope of developing potent anti-inflammatory drugs. According to Gedawy et al. (2020), analogs with benzotiophenyl and carboxylic acid (44) inhibited COX-2 better than celecoxib (IC50 = 0.01 and 0.70 μM, respectively) with almost similar 5-LOX inhibition as compared to the reference drug licofelone (IC50 = 1.78 and 0.51 μM, respectively). Prodrugs of compound 44 (45 and 46 with % edema inhibition = 57 and 72%, respectively) with dual COX/LOX inhibition elicited a better anti-inflammatory effect than celecoxib (36%). Additional interactions of these analogs with COX-2 (Arg106 and Ser339) and 5-LOX (Leu368, Leu414, Ile415, and Phe421) could inspire additional modification in the subsequent series of pyrazole analogs with the anti-inflammatory potential.Antidepressant ActivityThe level of monoamine is etiologically relevant to several psychiatric diseases such as anxiety and depression (Özdemir et al., 2020). In principle, the inhibition of monoamine oxidase (MAO) provides a good assessment of the antidepressant property of new drug candidates (Fajemiroye et al., 2015). This flavin adenine dinucleotide (FAD)–dependent enzyme exists in two isoforms (MAO-A and MAO-B). The monoamines (serotonin and norepinephrine) often associated with the etiology of depression are principal substrates of MAO-A (Özdemir et al., 2020). Analogs with a positively charged pyrazole moiety at N1 (hydroxy or dihydroxy, phenyl, chloro, methoxy, or dimethoxy groups) showed higher selectivity to MAO-A than MAO-B.

The 4,5-dihydro-1H-pyrazoles (47 and 48) showed a considerable affinity with MAO-A amino acid residues (Ala68, Tyr69, Phe208, Tyr407, and Tyr444). The N1-benzenesulfonyl ring at the pyrazoline nucleus seems to mediate additional interactions with the side chain and backbone residues of amino acids at the binding pocket of MAO-A (Tripathi et al., 2018).

The analogs with halogen groups in the phenyl ring could also promote hydrophobic interactions with MAO-A. The replacement of a polar 4-hydroxyphenyl substituent in pyrazoline nucleus (47) for a bulky hydrophobic 1-naphthyl substituent (48) significantly reduced the antidepressant effect. The addition of the N1-acetyl group at the pyrazole nucleus in combination with polar substituents (49–53) appears to stabilize FAD bonding and improve efficacy. According to Chimenti et al. (2006), the presence of dimethoxyphenyl on the pyrazole ring lowered the MAO inhibition potency of compound 51 (IC50 = 1.0 × 10–7 M) as compared with hydroxyphenyl radical in compound 52 (IC50 = 8.8 × 10–9 M). The incorporation of functional groups capable of increasing strain energy and facilitating ring-opening could increase the potency drastically. In this manner, the 4,5-dihydro-1H-pyrazole appears to be a better template for the design of MAO-A inhibitor (Chimenti et al., 2004; Tripathi et al., 2016; Upadhyay et al., 2017) than MAO-B inhibitor (Manna et al., 2002). The tautomeric forms of pyrazole by the active site of the enzyme play a key role in the development of antidepressant drugs (Secci et al., 2011). Altogether, many analogs are still without data on potency, efficacy, and MAO-A/MAO-B selectivity index that allow for comparative analysis and determination of the rational template for new pyrazole analogs with the antidepressant property. Although MAO inhibition offers a viable antidepressant mechanism, further screening of these analogs in the models of obsessive-compulsive, panic, anxiety disorder, and post-traumatic stress disorders could expand their potential applications, contraindications, and adverse events in the psychiatry setting.Other ActivitiesThe modulation of central and peripheral targets by the pyrazole ring and aforementioned moieties may induce diverse autonomic manifestations. Alteration in the activity of the autonomic nervous system could impact cardiac, vascular, and respiratory functions. The pyrazole-induced endothelium-dependent vascular relaxation, sympathoinhibition, and suppression of bronchial remodeling suggest cardiovascular or respiratory effects (Girodet et al., 2013; Fajemiroye et al., 2014; Basu et al., 2017; Menegatti et al., 2019). Compounds 54 and 55 with antihypertensive properties possess a piperazine ring with carboxylic acid or phenyl substituents, respectively. The introduction of 3,5-bis(trifluoromethyl) backbone with electron-withdrawing substituents in compounds 56 (37-fold Orai1 pore inhibition potency) and 57 (18-fold transient receptor potential canonical type 3 suppression potency) reduced respiratory impairments (Schleifer et al., 2012). Bronchial remodeling suppression with details on the efficacy, potency, selectivity, or mechanism of action has been reported for calcium-activated potassium channel blocker (58) and adenosine receptor subtype 2A inhibitor (59) with chloro or a meta-trifluoromethoxy substituent on the phenyl ring, respectively (Girodet et al., 2013; Basu et al., 2017).Some of the analogs that share the presence of electron-withdrawing groups in common tend to interact with inflammatory mediators that are relevant to gastrointestinal and metabolic disorders. Some of these analogs inhibit COX enzymes and suppress the synthesis of prostaglandin. Although both COX-1 and COX-2 isoforms are involved in homeostatic functions, the gastrointestinal ulceration of nonsteroidal anti-inflammatory drugs (NSAIDs) has been attributed to COX-1 inhibition and subsequent reduction in gastroprotective prostaglandin (Kanno and Moayyedi, 2020). Hence, pyrazole analogs with little or no effect on prostaglandin synthesis and release remain a viable therapeutic option in patients that are highly susceptible to NSAID-induced ulceration. The anti-inflammatory and antiedematogenic pyrazole analog (60; 40% of edema inhibition) with a very low ulcerogenic index (UI = 60) as compared with phenylbutazone and indomethacin (UI = 275 and 300, respectively) appears promising (Maggio et al., 2001). Unlike compound 60, both phenylbutazone and indomethacin are traditional NSAIDs well known for reducing prostaglandin levels through reversible and nonselective COX inhibition. In the ethanol-induced ulcer model, the benzimidazole–pyrazole hybrids (61–66) with substitutions on both aromatic rings of the pyrazole moiety reduced the ulcer index (UI = 72–83).

The ortho-hydroxyl group on the phenyl ring seems to be involved in hydrogen bonding with the proton bomb (H+/K+ ATPase) since the highest binding affinity (–9.8 kcal/mole) reported for compound 64 was lost in compounds 63 and 66 with methoxy group replacement (Noor et al., 2017). The suppression of harmful gastrointestinal effects has been partially attributed to the meta-methyl substitution on the pyrazole ring. The mepirizole analog (67) with methoxy and methyl groups at meta and para-positions on a pyrimidine ring exhibited 93% gastroprotective activity. However, the replacement of the pyrazole ring of mepirizole considerably attenuated this effect (7% inhibition of ulcer formation) (Ikeda et al., 1996).

These data indicate that appropriate substitutions on the pyrazole ring could reinforce gastroprotection.The analogs that suppress pro-inflammatory mediators could also modulate insulin sensitivity and protect against metabolic syndrome. Insulin resistance, oxidative products, and atherogenic dyslipidemia are among metabolic abnormalities underlying diabetes. A molecular hybrid of rimonabant (68) with chloro and methoxy substitutions on the phenyl ring elicited a significant antidiabetic effect (Hernández-Vázquez et al., 2015; Hernández-Vázquez et al., 2017).

In a separate study, the water-soluble pyrazole curcumin analog (69) inhibited advanced glycation end products (AGEs) and eliminated excess glucose (Sribalan et al., 2017). The AGEs, oxidative derivatives resulting from diabetic hyperglycemia, are increasingly seen as a potential risk for islet β-cell injury, insulin resistance, and diabetes (Vlassara and Uribarri, 2014). Although, compound 69 seems to inhibit AGEs (IC50 = 56.24 μg/ml) better than the parent curcumin (IC50 = 79.34 μg/ml) and standard drug phloroglucinol (IC50 = 135.73 μg/ml) sufficient data for comparative analysis of these analogs is still lacking. The chronic nature of the metabolic syndrome that warrants prolonged and often indefinite medications (Rochlani et al., 2017) makes the development of new analogs a promising strategy against the burden of adverse effects and patient nonadherence.Final Considerations and Future PerspectiveThe hunt for new analogs with desirable pharmacological profiles is a never-ending task in drug discovery programs. With the available literature on pyrazole analogs (Fadaly et al., 2020; Mohamed et al., 2020; Azimi et al., 2021; Faudzi et al., 2021; Verma et al., 2021), it is relatively easy for medicinal chemists to proceed with rational synthesis or modification capable of enhancing biological activities. The substitutions, additions, or removal of functional groups are effective strategies for designing biologically important analogs. The presence of new chemical entities could lead to additional or loss of molecular interactions. Cellular proliferation and metabolic enzymes provide important cytotoxic, cytoprotective, antinociceptive, anti-inflammatory, and antidepressant targets. However, specific contributions of the pyrazole ring and functional groups to these biological activities remain largely unclear.In light of this review, promising cytotoxic activities of some analogs against breast cancer cell lines (MCF-7 and MDA-MB-231) is expected to stimulate extensive evaluation of their effects on lung cancer (A-549), liver cancer (HepG-2), and brain cancer (HeLa) cell lines (Lv et al., 2016; Lehmann et al., 2017; Turkan et al., 2018; McKenzie et al., 2019; Bennani et al., 2020; Masaret, 2021). As a life-threatening health issue and one of the most lethal diseases known, cancer can be managed by targeting gene expression, certain protein synthesis, functions of organelles, pH, and electrolytes (Johnston and Strobel, 2020). For instance, the cytotoxic hypothesis appears to favor exposure to halogenated analogs capable of increasing halogen influx. This small-sized functional group with high electronegativity could lower cytosolic pH (cellular acidification). According to Johnston and Strobel (2020), increasing acidification and electrolyte imbalance by fluoride could disrupt metabolic processes and induce stress signaling, underpinning cellular toxicity. However, a detailed investigation of the level of analog-induced changes in redox reactions, oxidative stress, inflammation, glycation, and other metabolic processes could facilitate the repositioning of cytotoxic analogs for cytoprotection, and vice versa. Altogether, these effects may impact autonomic and central components vis-à-vis cardiovascular, cardiopulmonary, metabolic, and affective manifestations.Since antiproliferative and anti-inflammatory properties could reduce cellular infiltration and modulate gastrointestinal aggressive factors underlying peptic ulcer complications, in hypothesis, some pyrazole analogs could attenuate gastric ulceration, or in association with NSAIDs at subtherapeutic doses without loss of efficacy. The growing number of synthesized analogs without data of biological activity, mechanism of action, and comparative study with standard drugs containing the pyrazole ring (Hill and Whelan, 1980; Kameyama et al., 1981; Clemett and Goa, 2000; Samat et al., 2008; Straube, 2012; Dopp et al., 2013; Mitou et al., 2015; Karrouchi et al., 2018) may yield promising results, if evaluated in the future research.As the pyrazole moiety offers a central motif to different functional groups (Basu et al., 2017; Noor et al., 2017; Tripathi et al., 2018; Murahari et al., 2019; Kenchappa and Bodke, 2020), its simplified synthetic routes and potential activities are expected to continue to inspire additional chemical modifications (Johnston and Strobel, 2020) toward clinical applications. Emerging analogs with unique physicochemical, pharmacokinetic, and pharmacodynamic properties could be useful scaffolds for future studies. The aforementioned target interactions revealed how structural modification could enrich mechanistic studies. In the future, toxicological studies, reversibility, and selectivity of the effect of these analogs as well as the potential pharmacokinetic and pharmacodynamic interactions with other drugs are expected to predict adverse and therapeutic effects.Author ContributionsJF contributed to the conception, design, and writing of the work. LT contributed to the writing, revision, discussion, and drafting of the final work.

RC, KC, IRJ, LR, HN, PC, MN, and JM contributed to the writing, revision, and discussion. GG contributed to the drafting of chemical structures, analysis of chemical modification, and discussion. RM contributed to the analysis of chemical modification and critical revision for important intellectual content. GP, CX, and EC contributed to the discussion and critical revision.FundingThe authors appreciate all the institutional supports through Convênio UFG—UniEvangélica, FAPEG, CAPES, and CNPq.Conflict of InterestThe authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.Supplementary MaterialThe Supplementary Material for this article can be found online at: A. H., El-Din, A. G. S., El-Saadi, M. T., El-Moghazy, S. M., and Amin, N. H. (2020). Design, Synthesis and Biological Evaluation of Diarylpyrazole/triazole Bearing 1,3,4- Oxadiazole Moiety as Coxs Inhibitors Endowed with Potential Anti-inflammatory and Analgesic Activities. Rese. Jour. Pharm. Technol. 13 (9), 4255–4262. doi:10.5958/0974-360X.2020.00751.9CrossRef Full Text | Google ScholarAbdellatif, K. R.
A., Fadaly, W. A. A., Mostafa, Y. A., Zaher, D. M., and Omar, H. A. (2019). Thiohydantoin Derivatives Incorporating a Pyrazole Core: Design, Synthesis and Biological Evaluation as Dual Inhibitors of Topoisomerase-I and Cycloxygenase-2 with Anti-cancer and Anti-inflammatory Activities. Bioorg. Chem. 91, 103132. doi:10.1016/j.bioorg.2019.103132 PubMed Abstract | CrossRef Full Text | Google ScholarAbdellatif, K.
R. A., Abdelall, E. K. A., Lamie, P. F., Labib, M. B., El-Nahaas, E.-S., and Abdelhakeem, M.
M.
(2020). New Pyrazole Derivatives Possessing Amino/methanesulphonyl Pharmacophore with Good Gastric Safety Profile: Design, Synthesis, Cyclooxygenase Inhibition, Anti-inflammatory Activity and Histopathological Studies. Bioorg. Chem. 95, 103540. doi:10.1016/j.bioorg.2019.103540 PubMed Abstract | CrossRef Full Text | Google ScholarAl-Omar, M. A. (2010). Synthesis and Antimicrobial Activity of New 5-(2-Thienyl)-1,2,4-Triazoles and 5-(2-Thienyl)-1,3,4-Oxadiazoles and Related Derivatives. Molecules 15, 502–514. doi:10.3390/molecules15010502 PubMed Abstract | CrossRef Full Text | Google ScholarAzimi, F., Azizian, H., Najafi, M., khodarahmi, G., hassanzadeh, M., Saghaei, L., et al. (2021).
Design and Synthesis of Novel Pyrazole-Benzofuran Hybrids: In Vitro α-glucosidase Inhibitory Activity, Kinetic and Molecular Modeling Study.
Res. Square. doi:10.21203/rs.3.rs-288227/v1CrossRef Full Text | Google ScholarAziz, H., Zahoor, A. F., and Ahmad, S. (2020). Pyrazole Bearing Molecules as Bioactive Scaffolds: a Review. J. Chil.
Chem. Soc. 65 (1), 4746–4753. doi:10.4067/S0717-97072020000104746CrossRef Full Text | Google ScholarBadavath, V. N., and Jayaprakash, V. (2020). MAO Inhibitory Activity of 4,5-dihydro-1HPyrazole Derivatives: A Platform to Design Novel Antidepressants. Front. Drug Des. Discov. 1, 45. doi:10.2174/9789811421563121100005 Google ScholarBasu, S., Barawkar, D. A., Ramdas, V., Patel, M., Waman, Y., Panmand, A., et al. (2017). Design and Synthesis of Novel Xanthine Derivatives as Potent and Selective A 2B Adenosine Receptor Antagonists for the Treatment of Chronic Inflammatory Airway Diseases. Eur. J. Med.
Chem. 134, 218–229. doi:10.1016/j.ejmech.2017.04.014 PubMed Abstract | CrossRef Full Text | Google ScholarBennani, F. E., Doudach, L., Cherrah, Y., Ramli, Y., Karrouchi, K., Ansar, M. h., et al. (2020). Overview of Recent Developments of Pyrazole Derivatives as an Anticancer Agent in Different Cell Line. Bioorg. Chem. 97, 103470.
doi:10.1016/j.bioorg.2019.103470 PubMed Abstract | CrossRef Full Text | Google ScholarChimenti, F., Bolasco, A., Manna, F., Secci, D., Chimenti, P., Befani, O., et al. (2004). Synthesis and Selective Inhibitory Activity of 1-Acetyl-3,5-Diphenyl-4,5-Dihydro-(1h)-Pyrazole Derivatives against Monoamine Oxidase.
J. Med. Chem. 47 (8), 2071–2074. doi:10.1021/jm031042b PubMed Abstract | CrossRef Full Text | Google ScholarChimenti, F., Bolasco, A., Manna, F., Secci, D., Chimenti, P., Granese, A., et al. (2006). Synthesis, Biological Evaluation and 3D-QSAR of 1,3,5-Trisubstituted-4,5- Dihydro-(1h)-Pyrazole Derivatives as Potent and Highly Selective Monoamine Oxidase A Inhibitors. CMC 13 (12), 1411–1428. doi:10.2174/092986706776872907CrossRef Full Text | Google Scholarde Oliveira, L. P., da Silva, D. P. B., Florentino, I. F., Fajemiroye, J. O., de Oliveira, T. S., Marcelino, R. I. d. Á., et al. (2017).
New Pyrazole Derivative 5-[1-(4-Fluorophenyl)-1h-Pyrazol-4-Yl]-2h-Tetrazole: Synthesis and Assessment of Some Biological Activities. Chem. Biol. Drug Des. 89 (1), 124–135.
doi:10.1111/cbdd.12838 PubMed Abstract | CrossRef Full Text | Google ScholarDopp, J. M., Agapitov, A. V., Sinkey, C. A., Haynes, W. G., and Phillips, B. G.
(2013). Sildenafil Increases Sympathetically Mediated Vascular Tone in Humans. Am. J. Hypertens 26 (6), 762–769.
doi:10.1093/ajh/hpt018 PubMed Abstract | CrossRef Full Text | Google ScholarEl Shehry, M. F., Ewies, E. F., and Zayed, E. M. (2019). Synthesis of New Pyrazole Derivatives, Their Anti-inflammatory and Analgesic Activities, and Molecular Docking Studies. Russ. J. Gen. Chem. 89, 492–498. doi:10.1134/S1070363219030216CrossRef Full Text | Google ScholarFadaly, W. A. A., Elshaier, Y.
A. M. M., Hassanein, E.
H. M., and Abdellatif, K.
R. A. (2020). New 1,2,4-triazole/pyrazole Hybrids Linked to Oxime Moiety as Nitric Oxide Donor Celecoxib Analogs: Synthesis, Cyclooxygenase Inhibition Anti-inflammatory, Ulcerogenicity, Anti-proliferative Activities, Apoptosis, Molecular Modeling and Nitric Oxide Release Studies. Bioorg. Chem. 98, 103752. doi:10.1016/j.bioorg.2020.103752 PubMed Abstract | CrossRef Full Text | Google ScholarFaisal, M., Saeed, A., Hussain, S., Dar, P., and Larik, F. A. (2019). Recent Developments in Synthetic Chemistry and Biological Activities of Pyrazole Derivatives. J.
Chem. Sci. 131, 70.
doi:10.1007/s12039-019-1646-1CrossRef Full Text | Google ScholarFajemiroye, J. O., Amaral, N. O., da Silva, E. F., Galdino, P. M., de Oliveira, T. S., Ghedini, P. C., et al. (2014). Hypotensive and Antihypertensive Potential of 4-[(1-Phenyl-1h-Pyrazol-4-Yl) Methyl]1-Piperazine Carboxylic Acid Ethyl Ester: A Piperazine Derivative. Life Sci. 112 (1–2), 90–96. doi:10.1016/j.lfs.2014.07.025 PubMed Abstract | CrossRef Full Text | Google ScholarFajemiroye, J. O., Polepally, P. R., Chaurasiya, N. D., Tekwani, B.
L., Zjawiony, J. K., and Costa, E. A. (2015). Oleanolic Acid Acrylate Elicits Antidepressant-like Effect Mediated by 5-HT1A Receptor. Sci. Rep. 5, 11582. doi:10.1038/srep11582 PubMed Abstract | CrossRef Full Text | Google ScholarFaria, J.
V., Vegi, P. F., Miguita, A. G. C., Dos Santos, M. S., Boechat, N., and Bernardino, A. M. R. (2017). Recently Reported Biological Activities of Pyrazole Compounds. Bioorg. Med. Chem. 25 (21), 5891–5903. doi:10.1016/j.bmc.2017.09.035 PubMed Abstract | CrossRef Full Text | Google ScholarFaudzi, S. M. M., Leong, S.
W., Auwal, F. A., Abas, F., Wai, L. K., Ahmad, S., et al. (2021). In Silico studies, Nitric Oxide, and Cholinesterases Inhibition Activities of Pyrazole and Pyrazoline Analogs of Diarylpentanoids. Arch.
Pharm. 354, e2000161. doi:10.1002/ardp.202000161CrossRef Full Text | Google ScholarFlorentino, I. F., Silva, D. P. B., Cardoso, C. S., Menegatti, R., de Carvalho, F. S., Lião, L. M., et al. (2019). Antinociceptive Effects of New Pyrazoles Compounds Mediated by the ASIC-1α Channel, TRPV-1 and μMOR Receptors.
Biomed. Pharmacother. 115, 108915. doi:10.1016/j.biopha.2019.108915 PubMed Abstract | CrossRef Full Text | Google ScholarGalvão, G. M., Florentino, I.
F., Sanz, G., Vaz, B. G., Lião, L. M., Sabino, J. R., et al. (2020). Anti-inflammatory and Antinociceptive Activity Profile of a New Lead Compound - LQFM219. Int. Immunopharmacol. 88, 106893. doi:10.1016/j.intimp.2020.106893 PubMed Abstract | CrossRef Full Text | Google ScholarGameiro, I., Michalska, P., Tenti, G., Cores, Á., Buendia, I., Rojo, A. I., et al.
(2017). Discovery of the First Dual GSK3β inhibitor/Nrf2 Inducer. A New Multitarget Therapeutic Strategy for Alzheimer's Disease.
Sci. Rep. 7, 45701. doi:10.1038/srep45701 PubMed Abstract | CrossRef Full Text | Google ScholarGedawy, E. M., Kassab, A. E., and El Kerdawy, A. M.
(2020). Design, Synthesis and Biological Evaluation of Novel Pyrazole Sulfonamide Derivatives as Dual COX-2/5-LOX Inhibitors. Eur. J. Med. Chem.
189, 112066. doi:10.1016/j.ejmech.2020.112066 PubMed Abstract | CrossRef Full Text | Google ScholarGirodet, P.-O., Ozier, A., Carvalho, G., Ilina, O., Ousova, O., Gadeau, A.-P., et al. (2013).
Ca2+-Activated K+Channel-3.1 Blocker TRAM-34 Attenuates Airway Remodeling and Eosinophilia in a Murine Asthma Model. Am. J. Respir. Cell Mol. Biol. 48 (2), 212–219. doi:10.1165/rcmb.2012-0103OC10.1165/rcmb.2012-0103oc PubMed Abstract | CrossRef Full Text | Google ScholarHassan, G. S., Abdel Rahman, D. E., Abdelmajeed, E. A., Refaey, R. H., Alaraby Salem, M., and Nissan, Y. M. (2019). New Pyrazole Derivatives: Synthesis, Anti-inflammatory Activity, Cycloxygenase Inhibition Assay and Evaluation of mPGES. Eur. J. Med. Chem. 171, 332–342. doi:10.1016/j.ejmech.2019.03.052 PubMed Abstract | CrossRef Full Text | Google ScholarHe, B., Lu, C., Zheng, G., He, X., Wang, M., Chen, G., et al. (2016). Combination Therapeutics in Complex Diseases. J. Cell Mol.
Med. 20 (12), 2231–2240. doi:10.1111/jcmm.12930 PubMed Abstract | CrossRef Full Text | Google ScholarHernández-Vázquez, E., Castañeda-Arriaga, R., Ramírez-Espinosa, J. J., Medina-Campos, O. N., Hernández-Luis, F., Chaverri, J. P., et al. (2015). 1,5-Diarylpyrazole and Vanillin Hybrids: Synthesis, Biological Activity and DFT Studies. Eur. J. Med. Chem. 100, 106–118. doi:10.1016/j.ejmech.2015.06.010 PubMed Abstract | CrossRef Full Text | Google ScholarHernández-Vázquez, E., Ocampo-Montalban, H., Cerón-Romero, L., Cruz, M., Gómez-Zamudio, J., Hiriart-Valencia, G., et al.
(2017). Antidiabetic, Antidyslipidemic and Toxicity Profile of ENV-2: A Potent Pyrazole Derivative against Diabetes and Related Diseases. Eur. J. Pharmacol. 803, 159–166. doi:10.1016/j.ejphar.2017.03.036 PubMed Abstract | CrossRef Full Text | Google ScholarHill, B. T., and Whelan, R. D. H. (1980). Antitumour Activity and Cell Kinetic Effects of Pyrazofurin In Vitro. Eur. J. Cancer (1965) 16 (12), 1633–1638. doi:10.1016/0014-2964(80)90039-0CrossRef Full Text | Google ScholarHrelia, P., Sita, G., Ziche, M., Ristori, E., Marino, A., Cordaro, M., et al. (2020). Common Protective Strategies in Neurodegenerative Disease: Focusing on Risk Factors to Target the Cellular Redox System. Oxid. Med. Cell. Longev. 2020, 1–18. doi:10.1155/2020/8363245 PubMed Abstract | CrossRef Full Text | Google ScholarIkeda, M., Maruyama, K., Nobuhara, Y., Yamada, T., and Okabe, S.
(1996). Synthesis and Cytoprotective Antiulcer Activity of 2- or 4-(lH-Pyrazol-1-Yl)pyrimidine Derivatives Related to Mepirizole and Dulcerozine. Chem. Pharm. Bull. 44 (9), 1700–1706. doi:10.1248/cpb.44.1700 PubMed Abstract | CrossRef Full Text | Google ScholarKamel, M. (2015). Convenient Synthesis, Characterization, Cytotoxicity and Toxicity of Pyrazole Derivatives. ACSi 62 (1), 136–151. doi:10.17344/acsi.2014.828CrossRef Full Text | Google ScholarKameyama, T., Nabeshima, T., Yoshida, N., and Yamaguchi, K. (1981). Neurochemical Studies of an Analgesic, 1,3-Diphenyl-5-(2-Dimethylaminopropionamide)-Pyrazole [difenamizole]. Res. Commun. Chem. Pathol.
Pharmacol. 31 (1), 31–53.PubMed Abstract | Google ScholarKang, J. M., Kwon, S. O., Ann, J., Blumberg, P. M., Ha, H., Yoo, Y. D., et al. (2020). Discovery of 1-(1h-Indazol-4-Yl)-3-((1-Phenyl-1h-Pyrazol-5-Yl)methyl) Ureas as Potent and Thermoneutral TRPV1 Antagonists. Bioorg. Med. Chem. Lett. 30 (23), 127548. doi:10.1016/j.bmcl.2020.127548 PubMed Abstract | CrossRef Full Text | Google ScholarKarrouchi, K., Radi, S., Ramli, Y., Taoufik, J., Mabkhot, Y., Al-aizari, F., et al. (2018). Synthesis and Pharmacological Activities of Pyrazole Derivatives: A Review.
Molecules 23 (1), 134. doi:10.3390/molecules23010134 PubMed Abstract | CrossRef Full Text | Google ScholarKenchappa, R., and Bodke, Y. D.
(2020). Synthesis, Analgesic and Anti-inflammatory Activity of Benzofuran Pyrazole Heterocycles. Chem. Data Collec. 28, 100453. doi:10.1016/j.cdc.2020.100453CrossRef Full Text | Google ScholarKhalifa, N. M., Fahmy, H. H., Nossier, E. S., Amr, A. E., and Herqash, R. N. (2019). Novel Synthesis of Pyrazole-Containing Thiophene, 2-alkyloxypyridine and Thieno[2,3-D]pyrimidine Scaffolds as Analgesic Agents. Bull. Chem.
Soc. Ethiop. 33 (3), 505–515.
doi:10.4314/bcse.v33i3.11CrossRef Full Text | Google ScholarLehmann, T. P., Kujawski, J., Kruk, J., Czaja, K., Bernard, M. K., and Jagodzinski, P. P. (2017). Cell-specific Cytotoxic Effect of Pyrazole Derivatives on Breast Cancer Cell Lines MCF7 and MDA-MB-231.
J. Physiol. Pharmacol. 68 (2), 201–207.PubMed Abstract | Google ScholarLv, X.-H., Ren, Z.-L., Zhou, B.-G., Li, Q.-S., Chu, M.-J., Liu, D.-H., et al. (2016). Discovery of N-(benzyloxy)-1,3-diphenyl-1H-pyrazole-4-carboxamide Derivatives as Potential Antiproliferative Agents by Inhibiting MEK. Bioorg. Med. Chem. 24 (19), 4652–4659.
doi:10.1016/j.bmc.2016.08.002 PubMed Abstract | CrossRef Full Text | Google ScholarMaggio, B., Daidone, G., Raffa, D., Plescia, S., Mantione, L., Cutuli, V. M.
C., et al. (2001). Synthesis and Pharmacological Study of Ethyl 1-methyl-5-(substituted 3,4-Dihydro-4-Oxoquinazolin-3-Yl)-1h-Pyrazole-4-Acetates. Eur. J. Med. Chem. 36 (9), 737–742. doi:10.1016/s0223-5234(01)01259-4 PubMed Abstract | CrossRef Full Text | Google ScholarManna, F., Chimenti, F., Bolasco, A., Secci, D., Bizzarri, B., Befani, O., et al. (2002). Inhibition of Amine Oxidases Activity by 1-Acetyl-3,5-Diphenyl-4,5-Dihydro-(1h)-Pyrazole Derivatives. Bioorg. Med.
Chem. Lett. 12 (24), 3629–3633. doi:10.1016/s0960-894x(02)00699-6 PubMed Abstract | CrossRef Full Text | Google ScholarMasaret, G. S. (2021).
A New Approach for the Synthesis and Biological Activities of Novel Thiazolyl-Pyrazole Derivatives. ChemistrySelect 6, 974–982.
doi:10.1002/slct.202004304CrossRef Full Text | Google ScholarMcKenzie, J. A., Barghash, R. F., Alsaggaf, A. T., Kulkarni, O., Boudreau, K., Menard, F., et al. (2019). Synthesis and Evaluation of Novel Pyrazole Ethandiamide Compounds as Inhibitors of Human THP-1 Monocytic Cell Neurotoxicity. Cells 8 (7), 655. doi:10.3390/cells8070655 PubMed Abstract | CrossRef Full Text | Google ScholarMenegatti, R., Carvalho, F. S., Lião, L. M., Villavicencio, B., Verli, H., Mourão, A. A., et al. (2019).
Novel Choline Analog 2-(4-((1-Phenyl-1h-Pyrazol-4-Yl)methyl)piperazin-1-Yl)ethan-1-Ol Produces Sympathoinhibition, Hypotension, and Antihypertensive Effects.
Naunyn-schmiedeberg's Arch. Pharmacol. 392, 1071–1083. doi:10.1007/s00210-019-01649-8CrossRef Full Text | Google ScholarMitou, G., Frentzel, J., Desquesnes, A., Le Gonidec, S., AlSaati, T., Beau, I., et al. (2015). Targeting Autophagy Enhances the Anti-tumoral Action of Crizotinib in ALK-Positive Anaplastic Large Cell Lymphoma. Oncotarget 6 (30), 30149–30164. doi:10.18632/oncotarget.4999 PubMed Abstract | CrossRef Full Text | Google ScholarMohamed, H. H. M., Hussien, A. B. W. E. M., and Saeed, A. E. M. (2020). In Silico evaluation and Docking Studies of Pyrazole Analogs as Potential Autophagy Modulators against Pancreatic Cancer Cell Line MIA PaCa-2.
Eur. J. Chem. 11 (3), 187–193. doi:10.5155/eurjchem.11.3.187-193.1976CrossRef Full Text | Google ScholarMurahari, M., Mahajan, V., Neeladri, S., Kumar, M. S., and Mayur, Y. C. (2019). Ligand Based Design and Synthesis of Pyrazole Based Derivatives as Selective COX-2 Inhibitors. Bioorg.
Chem. 86, 583–597.
doi:10.1016/j.bioorg.2019.02.031 PubMed Abstract | CrossRef Full Text | Google ScholarNoor, A., Qazi, N. G., Nadeem, H., Khan, A.-u., Paracha, R. Z., Ali, F., et al. (2017). Synthesis, Characterization, Anti-ulcer Action and Molecular Docking Evaluation of Novel Benzimidazole-Pyrazole Hybrids. Chem. Cent. J. 11 (1). doi:10.1186/s13065-017-0314-0 PubMed Abstract | CrossRef Full Text | Google ScholarOliveira, D. H., Sousa, F. S. S., Birmann, P. T., Alves, D., Jacob, R. G., and Savegnago, L. (2020). Antinociceptive and Anti-inflammatory Effects of 4-(arylchalcogenyl)-1h-Pyrazoles Containing Selenium or Sulfur. Pharmacol. Rep.
72, 36–46. doi:10.1007/s43440-019-00001-4 PubMed Abstract | CrossRef Full Text | Google ScholarÖzdemir, Z., Alagöz, M. A., Uslu, H., Karakurt, A., Erikci, A., Ucar, G., et al. (2020). Synthesis, Molecular Modelling and Biological Activity of Some Pyridazinone Derivatives as Selective Human Monoamine Oxidase-B Inhibitors.
Pharmacol. Rep. 72, 692–704. doi:10.1007/s43440-020-00070-10.1007/s43440-020-00070-w PubMed Abstract | CrossRef Full Text | Google ScholarPatil, S. B. (2020). Medicinal Significance of Pyrazole Analogues: A Review.
J. Pharm. Sci.
Res. 12 (3), 402–404. Google ScholarRamsay, R. R., Popovic-Nikolic, M. R., Nikolic, K., Uliassi, E., and Bolognesi, M. L. (2018). A Perspective on Multi-target Drug Discovery and Design for Complex Diseases. Clin. Transl. Med. 7 (1), 3. doi:10.1186/s40169-017-0181-2 PubMed Abstract | CrossRef Full Text | Google ScholarRan, F., Liu, Y., Zhang, D., Liu, M., and Zhao, G. (2019). Discovery of Novel Pyrazole Derivatives as Potential Anticancer Agents in MCL. Bioorg. Med. Chem. Lett. 29 (9), 1060–1064. doi:10.1016/j.bmcl.2019.03.005 PubMed Abstract | CrossRef Full Text | Google ScholarRochlani, Y., Pothineni, N. V., Kovelamudi, S., and Mehta, J. L. (2017). Metabolic Syndrome: Pathophysiology, Management, and Modulation by Natural Compounds. Ther. Adv. Cardiovasc. Dis. 11 (8), 215–225. doi:10.1177/1753944717711379 PubMed Abstract | CrossRef Full Text | Google ScholarSamat, A., Tomlinson, B., Taheri, S., and Thomas, G. (2008). Rimonabant for the Treatment of Obesity. Recent Pat.
Cardiovasc. Drug Discov. 3 (3), 187–193. doi:10.2174/157489008786264014 PubMed Abstract | CrossRef Full Text | Google ScholarSchleifer, H., Doleschal, B., Lichtenegger, M., Oppenrieder, R., Derler, I., Frischauf, I., et al. (2012). Novel Pyrazole Compounds for Pharmacological Discrimination between Receptor-operated and Store-operated Ca 2+

Entry Pathways. Br. J. Pharmacol. 167, 1712–1722. doi:10.1111/j.1476-5381.2012.02126.x PubMed Abstract | CrossRef Full Text | Google ScholarSecci, D., Bolasco, A., Chimenti, P., and Carradori, S. (2011). The State of the Art of Pyrazole Derivatives as Monoamine Oxidase Inhibitors and Antidepressant/anticonvulsant Agents. CMC 18 (33), 5114–5144. doi:10.2174/092986711797636090CrossRef Full Text | Google ScholarSribalan, R., Shakambari, G., Banuppriya, G., Varalakshmi, P., Subramanian, E. R., Sudhakar, S., et al. (2017). Synthesis of a Water-Soluble Pyrazole Curcumin Derivative:In VitroandIn VivoAGE Inhibitory Activity and its Mechanism. ChemistrySelect 2 (3), 1122–1128. doi:10.1002/slct.201601740CrossRef Full Text | Google ScholarStraube, S. (2012). Anti-inflammatory and Antipyretic Analgesics and Drugs Used in Gout. Side Effects Drugs Annu., 181–193. doi:10.1016/b978-0-444-59499-0.00009-xCrossRef Full Text | Google ScholarTaher, A. T., Mostafa Sarg, M. T., El-Sayed Ali, N. R., and Hilmy Elnagdi, N. (2019). Design, Synthesis, Modeling Studies and Biological Screening of Novel Pyrazole Derivatives as Potential Analgesic and Anti-inflammatory Agents. Bioorg. Chem. 89, 103023. doi:10.1016/j.bioorg.2019.103023 PubMed Abstract | CrossRef Full Text | Google ScholarToral-Rios, D., Pichardo-Rojas, P. S., Alonso-Vanegas, M., and Campos-Peña, V. (2020). GSK3β and Tau Protein in Alzheimer's Disease and Epilepsy. Front. Cell Neurosci. 14, 19. doi:10.3389/fncel.2020.00019 PubMed Abstract | CrossRef Full Text | Google ScholarToton, E., Ignatowicz, E., Bernard, M. K., Kujawski, J., and Rybczynska, M.
(2013). Evaluation of Apoptotic Activity of New Condensed Pyrazole Derivatives. J. Physiol.
Pharmacol. 64, 115–123.PubMed Abstract | Google ScholarTripathi, A. C., Upadhyay, S., Paliwal, S., and Saraf, S. K. (2016). An Expeditious One-Pot Microwave Facilitated versus Conventional Syntheses: In Vivo Biological Screening and Molecular Docking Studies of Some 3,5-Disubstituted-4,5-Dihydro-(1h)-Pyrazole Derivatives. Med. Chem. Res. 25, 390–406. doi:10.1007/s00044-015-1489-3CrossRef Full Text | Google ScholarTripathi, A. C., Upadhyay, S., Paliwal, S., and Saraf, S. K. (2018). Derivatives of 4,5-dihydro (1H) Pyrazoles as Possible MAO-A Inhibitors in Depression and Anxiety Disorders: Synthesis, Biological Evaluation and Molecular Modeling Studies. Med. Chem. Res. 27, 1485–1503. doi:10.1007/s00044-018-2167-zCrossRef Full Text | Google ScholarTurkan, F., Cetin, A., Taslimi, P., and Gulçin, İ. (2018). Some Pyrazoles Derivatives: Potent Carbonic Anhydrase, α-glycosidase, and Cholinesterase Enzymes Inhibitors. Arch. Pharm. Chem. Life Sci. 351 (10), e1800200. doi:10.1002/ardp.201800200CrossRef Full Text | Google ScholarUpadhyay, S., Tripathi, A. C., Paliwal, S., and Saraf, S. K. (2017). Facile One-Pot Synthesis Methodology for Nitrogen-Containing Heterocyclic Derivatives of 3,5-disubstituted 4,5-Dihydro-1h-Pyrazole, Their Biological Evaluation and Molecular Docking Studies.
Pharm. Chem. J. 51, 564–575. doi:10.1007/s11094-017-1655-7CrossRef Full Text | Google ScholarVerma, R., Verma, S. K., Rakesh, K.
P., Girish, Y. R., Ashrafizadeh, M., Sharath Kumar, K. S., et al. (2021). Pyrazole-based Analogs as Potential Antibacterial Agents against Methicillin-Resistance staphylococcus Aureus (MRSA) and its SAR Elucidation. Eur. J. Med.
Chem. 212, 113134. doi:10.1016/j.ejmech.2020.113134 PubMed Abstract | CrossRef Full Text | Google ScholarYet, L.
(2018). “Privileged Structures in Drug Discovery: Medicinal Chemistry and Synthesis,” in Methods and Principles in Medicinal Chemistry. London; Hoboken, NJ: John Wiley & Sons. doi:10.1002/9781118686263CrossRef Full Text | Google ScholarZhao, H.
(2007). Scaffold Selection and Scaffold Hopping in Lead Generation: a Medicinal Chemistry Perspective.
Drug Discov. Today 12 (3–4), 149–155. doi:10.1016/j.drudis.2006.12.003 PubMed Abstract | CrossRef Full Text | Google ScholarKeywords: heterocyclic ring, functional groups, derivatives, interactions, activitiesCitation: Costa RF, Turones LC, Cavalcante KVN, Rosa Júnior IA, Xavier CH, Rosseto LP, Napolitano HB, Castro PFdS, Neto MLF, Galvão GM, Menegatti R, Pedrino GR, Costa EA, Martins JLR and Fajemiroye JO (2021) Heterocyclic Compounds: Pharmacology of Pyrazole Analogs From Rational Structural Considerations. Front. Pharmacol. 12:666725. doi: 10.3389/fphar.2021.666725Received: 10 February 2021; Accepted: 23 April 2021;Published: 10 May 2021.Edited by:Syed Nasir Abbas Bukhari, Al Jouf University, Saudi ArabiaCopyright © 2021 Costa, Turones, Cavalcante, Rosa Júnior, Xavier, Rosseto, Napolitano, Castro, Neto, Galvão, Menegatti, Pedrino, Costa, Martins and Fajemiroye. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.*Correspondence: James Oluwagbamigbe Fajemiroye, jamesfajemiroye@ufg.br†These authors have contributed equally to this work and share first authorship People also looked at