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Synthesis of Novel 1,3,4, Oxadiazole from Chloro (amino pyrazoly) ketone carbohydrazide, their Fluorescence properties and Xanthine oxidase inhibitory activity

Chemistry

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ABSTRACT

In order to explore high strength organic electro transporting electroluminescent (EL) materials, three new pyrazole oxadiazole compounds containing the phenyl group in the 1st position of pyrazole, methyl group at 3rd position, (amino pyrazoly) ketone with 1,3,4 oxadiazole moiety contains various substituent in the 4th position and chloro group in the 5th position of pyrazole were synthesized. Their structures were characterized by IR, 1H NMR spectra and elemental analysis. A new method of synthesizing 1,3,4-oxadiazole compound was described showing fluorescence characteristic. The fluorescence properties were measured by fluorometry. And synthesized oxadiazole were tested for xanthine oxidase inhibitory activity against standard drug Allopurinol.

KEYWORDS:

Pyrazole-4-Carbohydrazide, Chloro (amino Pyrazoly) ketone, 1, 3, 4 Oxadiazole, Fluorescence property, XO inhibitory activity.

Introduction

1, 3, 4-oxadiazole has great unparalleled performance in electronic-injection and electronic transmission and possess various biological activities like antimicrobial[1], anti-inflammatory[2], antitubercular3, anti-convulsant[4], analgesic[5], anti-tumor activities[6].In the past decades, various attempts were made to elucidate the mechanism of fluorescence in these compounds by studying the effect of substituent on the absorption and fluorescence properties of this class of compounds [7-8]. The organic and polymer electroluminescence (EL) devices have show several advantages over inorganic ones, such as low cost, high luminous efficiency, wide selection of emission colors via molecular design of organic and polymer materials, and easy processing. In recent years, synthesis and study of pyrazole derivatives have become more and hotter in heterocyclic chemistry because pyrazole possesses good biological activity. Pyrazole derivatives are well known for their applications in fluorescence probes and pharmacological activities such as Antibacterial and antifungal [9], Antiviral [10], Antipyretic, antioxidant [11], anticancer [12], analgesics, anti-inflammatory [13], antidepressant and anticonvulsant activities[14].

Xanthine oxidase (XO) inhibitors have been widely used for the treatment of gout. Xanthine oxidase is a key enzyme that catalyses the oxidation of hypoxanthine and xanthine to generate uric acid in catabolic sequence of the purine nucleotide metabolism in humans and a few other uricotelic species[15]. Allopurinol, a purine analogue is the first XO inhibitor and has been widely used in clinical management of gout for several decades. Xanthine oxidase inhibitors such as allopurinol interfere with the conversion of hypoxanthine to xanthine and then to uric acid. In general, allopurinol is the drug of choice; however it has been observed that allopurinol induces side effects such as fever, skin rash, eosinophilia, hepatitis and worsened renal function[16]. Thus, new alternatives with an increased therapeutic activity and less side effects are desired. In the recent years, several synthetic skeletons containing thiazole, triazole pyrimidine have been reported to display XO inhibitory activity [17-19].

The modification of pyrazole and oxadiazole such as substituent moiety should provide potential fluorescence properties and biological activities. Although much efforts have been put into the synthesis and biological evaluation of pyrazoles and oxadiazoles and numerous corresponding derivatives with fluorescence properties and diverse biological activities. In this paper, three new pyrazole oxadiazole compounds were designed and synthesized. Their fluorescence properties were measured as quantum yield and the results showed that target compounds had good fluorescence and XO inhibitory activity tested of this pyrazole-based 1,3,4- oxadiazole derivatives against standard drug Allopurinol. The synthetic route of the target compounds shows in Scheme 1.

Experimental

Materials and methods

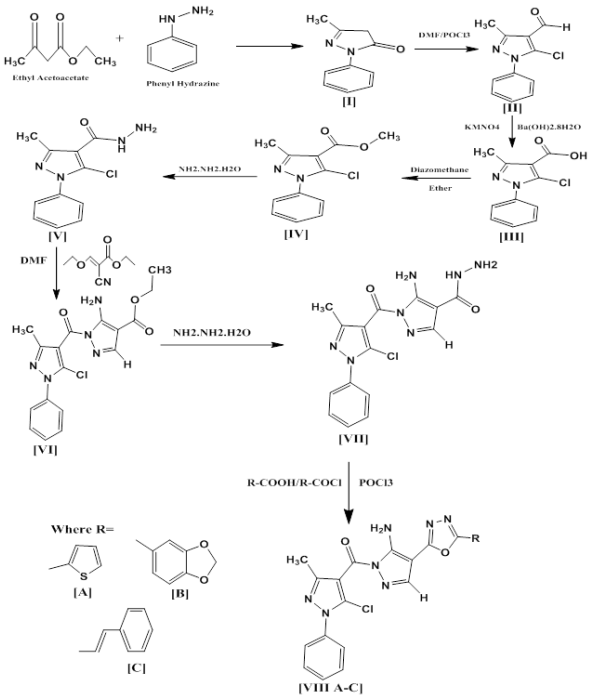
All melting points were obtained on a melting point apparatus and were uncorrected. All fluorescence spectra were recorded with a Flurolog Modular spectrofluorometer of Horiba scientific equipped with a 2 mm path length quartz cell and using quinine sulfate as a reference substance. All absorbance spectra were recorded with a Perkin Elmer Lambda 25 spectrophotometer equipped with a 2 mm path length quartz cell. 1 H NMR spectra were recorded with a Bruker-400 spectrometer with TMS as an internal standard in CDCl3/d6-DMSO. Infrared (IR) samples were prepared as KBr pellets and recorded on Perkin Elmer FTIR and only noteworthy absorption levels (cm^{-1}) are listed. Elemental analyses (C, H, N and S) were performed on a Perkin Elmer Model 2400 analyzer. Reaction progress was monitored by thin layer chromatography (TLC) using ethyl acetate/pet-ether as the mobile phase on pre-coated silica gel plates. 5-Chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-Carbohydrazide was prepared as per the procedure described in our research paper[20].

Ethyl (ethoxymethylene) cyanoacetate, hydrazine hydrate, phosphorus oxychloride, 2-thiophene carbonyl chloride, Piperonylic acid, Cinnamic acid were purchased from Alfa Aesar, SD Fine Chem and Sigma-Aldrich. Quinine, Allopurinol, Xanthine Oxidase Enzyme (5Unit/mg) was purchased from Sigma-Aldrich.

Synthesis of intermediates and target compounds

5-Methyl-2-phenyl-2, 4-dihydro-pyrazole-3-one [I]

50 gm (49 mL, 0.384 mole) of redistilled ethyl acetoacetate and 40 gm (36.5 mL, 0.37 mole) of phenyl hydrazine were mixed together in a large evaporating dish. The mixture was heated on a boiling water bath in the fume cupboard for about 2 hours and stirred from time to time with glass rod. The heavy reddish syrup was allowed to cool somewhat, about 100 mL. of ether was added to it and the mixture was stirred vigorously. The syrup, which was insoluble in ether, solidified within 15 minutes. The solid was filtered at the pump and washed thoroughly with ether to remove colored impurities. It was recrystallised from hot water to give 5-methyl-2-phenyl-2, 4-dihydro-pyrazole-3-one.



5-Chloro-3-methyl-1-phenyl-1 *H*-pyrazole-4-carbaldehyde [II]

For the preparation of 5-chloro-3-methyl-1-phenyl-1 *H*-pyrazole-4-carbaldehyde, $POCl^3$ (0.35 mole, 32.0 mL.) was added to ice-cold dimethyl formamide (0.16 mole, 12.0 mL.). To this mixture 5-methyl-2-phenyl-2,4-dihydro-pyrazol-3-one (0.05 mole, 8.1 gm) was added and the mixture was heated under reflux for 1.0 hrs. After cooling the reaction mixture was poured into ice-cold water (300 mL). The solid precipitated was collected by filtration, washed with cold water, dried and recrystallised from ethanol to give pale yellow crystal of 5-chloro-3-methyl-1-phenyl-1 *H*-pyrazole-4-carbaldehyde. Yield (90 %), mp: 145-148 °C.

5-Chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxylic Acid [III]

In three 500 mL flask, 5-chloro-3-methyl-1-phenyl-1 *H*-pyrazole-4-carbaldehyde 0.05 mol and 100 mL of water was slowly added dropwise 0.075 mol $KMnO^4$ in 200 mL aqueous oxidation. Dropping was completed, the temperature was raised to 70 -80 ° C reactor 8 h. Adjusting the pH of the reaction solution was made alkaline with 10% Barium Hydroxide solution was slowly cooled, insoluble's were removed by filtration, and the filtrate was acidified with concentrated hydrochloric acid, the precipitated white solid was suction filtered, washing and drying, a white solid; Yield: Yield- (70.0 %) mp: 230 °C.

5-Chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxylic Acid Methyl ester [IV]

2.365 gm (0.01 mole) of 5-chloro-3-methyl-1-phenyl-1 *H*-pyrazole-4-carboxylic acid was dissolved in 25 mL of ether. The solution was cooled to 0^0c, with proper precaution excess diazomethane solution was added. As the reaction continued nitrogen present in the solution bubbled out. The reaction mass was kept in refrigerator overnight. Excess diazomethane was distilled out. The solid precipitate of 5-chloro-3-methyl-1-phenyl-1 *H*-pyrazole-4-carboxylic acid methyl ester was recrystallized in ethanol. Yield- 75 % mp: 68 °C.

5-Chloro-3-methyl-1-phenyl-1 *H*-pyrazole-4-Carbohydrazide

2.0 gm of 5-chloro-3-methyl-1-phenyl-1 *H*-pyrazole-4-carboxylic acid methyl ester was kept overnight under reflux in 10.0 mL of hydrazine hydrate. 25.0 mL of chloroform was added to the reaction mass and the hydrazine hydrate layer was separated. The chloroform layer was washed thrice with water. The chloroform layer was dried on anhydrous sodium sulfate. The chloroform was evaporated to get solid precipitate of 5-chloro-3-methyl-1-phenyl-1 *H*-pyrazole-4-Carbohydrazide. It was recrystallized in ethanol. Yield- (60.0 %) mp: 172-175 °C.

Ethyl-5-amino-1-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbonyl)-1*H*-pyrazole-4-carboxylate [VI]

To a solution of 12.52 gm (0.05 mol) 5-chloro-3-methyl-1-phenyl-1[*H*]-pyrazole-4-carbohydazide [V] in 50 mL DMF is added 12.69 gm (0.075 mol) of Ethyl (ethoxymethylene) cyanoacetate. The mixture is refluxed for 8 h and cooled to room temperature. The precipitate solid is collected by filtration, wash with Ethanol and a white solid is obtained is than crystallized in Ethanol to gives Ethyl-5-amino-1-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbonyl)-1*H*-pyrazole-4-carboxylate [VI].

This compound is obtained as colorless white crystals (alcohol), yield 54 %, mp 236~238 °;

1H NMR (400 MHz, δ ppm, CDCl3): δ 0.85 ppm (t, 3H, $COOCH_2CH_3$); δ 2.1 ppm (d, 3H, CH_3); δ 3.85 ppm (q,2H $COOCH_2$); δ 5.45 ppm (s,2H,NH_2); δ 7.0-7.1 ppm (m,5H,ArH); δ 7.39 ppm (s,1H,-CH)

IR (potassium bromide): 900-675 — C—H stretching; 1097— Cl stretching; 1252.79— C—C=O-O stretching; 1375-1450— CH_3 bending; 1400-1450 — CH_2 bending; 1300-1600— Ring stretching vibration; 1590.34 — C=C stretching; 1719.57 —C=O stretching; 3211.53-3415.03 —Heteroaromatic N-H stretching

Anal. Calculated. for $C_{17}H_{16}ClN_5O_3$: C=54.63%; H=4.31%; N=18.74%
Found: C=53.51%; H=5.21%; N=18.00%

5-amino-1-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbonyl)-1*H*-pyrazole-4- carbohydrazide [VII]

A suspension of Ethyl-5-amino-1-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbonyl)-1*H*-pyrazole-4-carboxylate [VI] 7.5 gm (0.02 mol) in 25 mL 80% hydrazine hydrate is heated at 105° for 6 h. Then the solution is evaporated under vacuum and cooled to room temperature. The residue is filtrated; washed with 25 mL diethyl ether three times. A white crystalline solid of 5-amino-1-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbonyl)-1*H*-pyrazole-4-carbohydrazide [VI] is obtained.

This compound is obtained as colorless solid, yield 60 %; mp 292 °C.

1*H* NMR (400 MHz, δ ppm, DMSO): δ 2.5 ppm (s, 3H, CH_3); δ 4.5 ppm (s, 2H, $CONHNH_2$); δ 5.5 ppm (s,2H,NH_2); δ 7.5-7.7 ppm(m,5H,ArH); δ 8.15 ppm (s,1H,-CH); δ 9.6 ppm (s, 1H,-NH, D_2O Ex.)

IR (potassium bromide): 706.92 — C-Cl stretching; 1622.16 — C=C stretching in ring; 1655.92, 1696.42 — C=O stretching; 3211.53, 3285.79 — NH_2 stretching; 3432.39 — NH stretching
Anal. Calculated For $C_{15}H_{11}ClN_2O_2$: C=54.41%; H=3.61%; N= 15.86%
Found: C=55.10%; H=4.01%; N=16.50%

General method for the synthesis of 1, 3, 4 Oxadiazole of 5-amino-1-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbonyl)-1*H*-pyrazole-4- carbohydrazide with Aromatic and Heterocyclic Carboxylic Acid and Carbonyl Chloride [VIII A-C]

Reflux 0.72 gm (0.002 mol) of 5-amino-1-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbonyl)-1*H*-pyrazole-4-carbohydrazide with 0.0024 mole of corresponding aromatic or heterocyclic carboxylic acid or Chloride in 5 ml of Phosphoryl chloride for 4-5 Hrs. Cool the reaction mass and poured in crushed ice. Solid extracted twice with dichloromethane. Combined the organic layer wash with 5% sodium bicarbonate solution and then with water. Reaction progress was monitored by thin layer chromatography (TLC) using ethyl acetate/peter ether as the mobile phase on pre-coated silica gel plates. Dried the organic layer with on anhydrous sodium sulphate and evaporated Methylene dichloride to gives crude solid. Purified the crude solid on silica column chromatography using Hexane: Ethyl acetate (7:3) mobile phase to gives 1, 3, 4 oxadiazole of 5-amino-1-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbonyl)-1*H*-pyrazole-4-carbohydrazide [VIIIA-C], showing fluorescence properties.

Synthesis of (5-amino-4-(5-(thiophen-2-yl)-1,3,4-oxadiazol-2-yl)-1*H*-pyrazol-1-yl)(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl) methanone [VIII A]

This compound is obtained as light yellow solid, yield 35 %; mp 242°C (Decomposes)

1*H* NMR (400 MHz, δ ppm, CDCl3): δ 2.83 ppm (s,3H,CH_3); δ 5.5 ppm (s, 2H, NH_2); δ 7.2 ppm (t, 1H, 2-Thiophene); δ 7.5-7.6 ppm (m,5H,ArH); δ 7.8 ppm (d,2H, 2-Thiophene); δ 7.9 ppm (s,1H,-CH)

IR (potassium bromide): 688.60 — C-S stretching; 750.32, 800.74 — C-Cl stretching; 1490.04, 1584.87, 1572.98 — C=C stretching; 1722.46 — C=O stretching; 3020.58 — Aromatic C-H stretching; 3428.53 — NH_2 stretching

Calculated for $C_{20}H_{14}ClN_7O_2S$: C=53.16%; H=3.12%; N=21.70%;
Found : C=51.56 %; H=3.28 %; N=20.39 %;

Synthesis of 5-amino-4-(5-(benzo[d][1,3]dioxol-5-yl)-1,3,4-oxadiazol-2-yl)-1*H*-pyrazol-1-yl)(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methanone [VIII B]

This compound is obtained as brown solid, yield 30 %; mp 252°C (Decomposes)

1*H* NMR (400 MHz, δ ppm, CDCl3): δ 2.70 ppm (s,3H,CH_3); δ 5.50 ppm (s, 2H, NH_2); δ 6.05 ppm (d,2H, 1,3 Dioxole); δ 6.90 ppm (s,1H, 1,3 Dioxole); δ 7.50-7.70 ppm (m,5H,ArH); δ 7.80 ppm (q,2 H, 1,3 Dioxole); δ 7.9 ppm (s,1H,-CH)

IR (potassium bromide): 763.82 — C-Cl stretching; 1076.30, 1109.09 — C-O stretching Dioxole; 1673.28 — C=O stretching; 3058.91 — Heteroaromatic C-H stretching; 3430.46 — NH_2 stretching

Calculated for $C_{23}H_{16}ClN_7O_4$: C=56.39%; H=3.29%; N=20.02%
Found : C=55.09%; H=3.52%; N=19.17%

Synthesis of (E)-(5-amino-4-(5-styryl-1,3,4-oxadiazol-2-yl)-1*H*-pyrazol-1-yl) (5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl) methanone [VIII C]

This compound is obtained as brown solid, yield 32 %; mp 282 °C (Decomposes)

1*H* NMR (400 MHz, δ ppm, CDCl3): δ 2.7 ppm (s,3H,CH_3); δ 5.50 ppm (s, 2H, NH_2); δ 6.89 ppm (d,1H, -CH=); δ 7.00 ppm (d,1H,=CH-); δ 7.50-7.75 ppm (m,10 H, 5X2 ArH); δ 7.90 ppm (s,1H,-CH)

IR (potassium bromide): 799.51 — C-Cl stretching; 1628.91 — C=C stretching; 1693.53 — C=O stretching; 3060.12 — C-H stretching (Aromatic Ring Proton); 3402.49 — NH_2 stretching

Calculated for $C_{24}H_{18}ClN_7O_2$: C=61.09%; H=3.84%; N=20.78%
Found : C=59.19%; H=4.13%; N=19.78%

Results and discussion

Fluorescence Properties and Quantum Yield Calculation

$$Y_2 = Y_1 \frac{F_2}{F_1} \cdot \frac{A_1}{A_2}$$

Y1 and Y2 represent the fluorescence quantum yield of reference and target compounds, respectively. F1 and F2 represent the integral fluorescence intensity of reference and target compounds, respectively. A1 and A2 represent absorbance of incident light of reference and target compounds, respectively.

We use quinine sulfate as a reference substance (1 × 10–6 mol/L sulfuric acid solution of quinine sulfate) and the fluorescence quantum yield is 0.55. Fluorescent spectra characteristics of compounds with different concentrations is different, table 1 show that the fluorescent spectra characteristic is best when concentration of compound VIII A is 1 × 10–6 mol/L and the fluorescence quantum yields up to 0.27. At this concentration fluorescence quantum yield of VIII B and VIII C is 0.48 and 0.47 respectively.

Fluorescent spectra characteristics of compound with different polar solvent are different and the solvent effect is very important.

Table 1: shows the fluorescent spectra characteristics of A, B, C in chloroform and Dimethyl Formamide (DMF)

Quantum Yield							
Sr. No.	**Comp.**	**Solvent**	**λ EX/nm**	**λ EX2/nm**	**A**	**F**	**Y**
1	**Quinine**		349	450	0.10779	13502	0.55
2	**VIII A**	CHCl3	365	538	5.035	316000	0.27
3	**VIII B**	DMF	330	483	3.853	428000	0.48
4	**VIII C**	DMF	339	493	5.516	595000	0.47

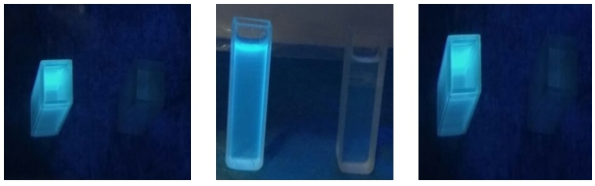


Fig.1 Fluorescence images of Compounds VIII (A-C) in Chloroform and DMF

The maximum fluorescence intensity and fluorescence yield in chloroform is the best it may be caused by the polar of compound A matching with the polarity of chloroform, however, the polarity of DMF is high, the dissolvability of compound VIII A in these solvents is not very good, so the fluorescent spectra characteristics of compound VIII A is not ideal when the solvent is DMF. But it is ideal in case of compound VIII B and VIII C, which showing good fluorescent spectra in DMF .

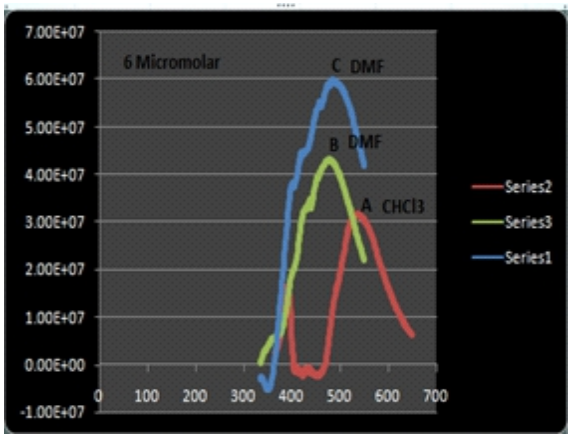


Fig.2 Fluorescent spectra of compound VIII A, B, C in Chloroform and DMF

XO inhibition assay

All the newly synthesized compounds were evaluated for their in vitro inhibitory activity against xanthine oxidase enzyme by spectrophotometrically measuring the formation of uric acid at 295 nm according to the reported method with some modifications as described below.

The Synthesized 1,3,4 Oxadiazole compounds and Allopurinol were dissolved in minimum amount of dimethylsulfoxide (DMSO). The assay mixture consisted of 50 mM potassium phosphate buffer (pH 7.4) (Prepare 200 mL in deionized water using Potassium Phosphate, monobasic, anhydrous. Adjust to pH 7.4 at 25°C with 1M KOH). 0.15

mM xanthine solution (prepare 100 mL by initially dissolving Xanthine by adding 2-3 drops of 1.0 M NaOH to increase the solubility. Add approximately 90 mL of deionized water. Adjust to pH 7.5 at 25°C with either 1 M NaOH or 1M HCl. Dilute to final volume of 100 mL). 0.05 units/mL of XO Enzyme solution (Immediately before use, prepare a solution containing 0.05 units/ml of Xanthine Oxidase in cold 50 mM Potassium Phosphate buffer).

The total volume of the assay mixture was 3.2 mL and consisting of 1 mL sample solution studied, 1 mL 0.15 M phosphate buffer (pH 7.4), 100 µL of the enzyme xanthine oxidase solution. After preincubation of the test solution at 37°C for 15 min, the reaction was initiated by addition 100 µL of xanthine substrate solution and incubated at 37°C for 30 min. The reaction was stopped by adding 1 mL of 1N HCl. The absorption was measured at 295 nm to indicate the formation of uric acid. All experiments were performed in triplicate and averaged. The percentage inhibitory activity of the samples were determined against a DMSO blank, and calculated by using the following formula. Allopurinol was used as Standard.

Inhibition (%) = 100 - [(OD test compound /OD control) × 100]

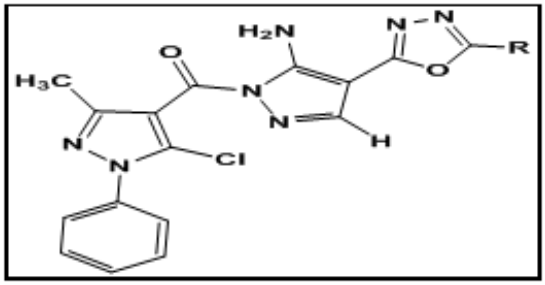
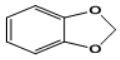


Table 2: In Vitro Xanthine oxidase inhibitory activity of compounds VIII (A-C) and Allopurinol

Compound	R	XO Inhibitory activity IC50 (µM)a
VIII A		75.60
VIII B		50.55
VIII C		>100
Allopurinol		2.6

Conclusion

Dissolvability of compound VIII A is showing good florescence spectra in Chloroform, so shows good florescence emission and the florescence spectra characteristic is best with this concentration. Florescence Quantum Yield is 0.27. Same as the compound VIII B & VIII C shows good florescence emission using DMF as a Solvent. The results showed that the target compounds had good fluorescence and λ em ranged from 410 nm to 550 nm and fluorescence quantum yields up to 0.48.

In addition, the in vitro inhibitory activity against xanthine oxidase was evaluated and compound VII A and VIII B was found to be the most active against commercial XO with IC50 value 75.60 mM and 50.55 mM respectively. Although the inhibitory activity was lower compared to that of the standard drug allopurinol, further optimization of substituted R groups which may obtain more potent XO inhibitors are in progress in our laboratory.

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References

1. Jaiswal N., Singh A. K., Singh D., Ahmad T. A.,(2012). Comprehensive review on antimicrobial activity of 1,3,4-oxadiazole derivatives. International Research Journal of Pharmaceutical, 3(3), 83-89.
2. Amir M., Saifullah K., Akhter W., (2011). Design, synthesis and pharmacological evaluation of 1,3,4-oxadiazole derivatives of aryl acrtic acid as anti-inflammatory and analgesic agents. Indian Journal of Chemistry, 50(B), 1107-1111.
3. Pattan S.R., Rabara P. A., Pattan J. S., Bukitagar A. A., Wakale V. S., Musmade D. S.,(2009). Synthesis and evaluation of some novel substituted 1,3,4-oxadiazole and pyrazole derivative for antitubercular activity. Indian Journal of Chemistry, 48(B), 1453-1456.
4. Singh P., Jangra P.K., (2010). Oxadiazole: A novel class of anticonvulsant agents. Der Chemica Sinica, 1(3), 118-123.
5. Dewangan D., Pandey A., Sivakumar T., Rajavel R., Dubey R. D.,(2010). Synthesis of some Novel 2,5-Disubstituted 1,3,4-oxadiazole and its Analgesis, Anti-inflammatory, Anti Bacterial and Anti-Tubercular Activity. International Journal of Chemical Technology Research 2(3), 1397-1412.
6. El-Hamouly W. S., Amin K. M., El-Assaly S. A., El-Meguid E. A. A.,(2011). Synthesis and antitumor activity of some new 1,3,4-oxadiazole,pyrazole and pyrazolo[3,4-d]pyramidine derivatives attached to 4-benzothiazol-2-yl phenyl moiety. Der Pharma Chemica, 3(6), 282-292.
7. Sandler S.R., Tosu K.C., (1963). Fluorescence spectral study of wavelength shifters for scintillation plastics. Journal of Chemical Physics, 39, 1062. doi: http://dx.doi.org/10.1063/1.1734359
8. Jina M., Liang Y. J., Lua R., Chuai X., Zhao X. Y., Zhang H. J., (2004) Synthesis and properties of photoluminescence of pyrazoline derivatives. Synthetic Metals 140, 37-41. doi:10.1016/S0379-6779(02)01320-6
9. Hassan S. Y., (2013) Synthesis, Antibacterial and antifungal activity of some new pyrazoline and pyrazole derivatives. Molecules, 18, 2683-2711. DOI:10.3390/molecules18032683
10. Guiping O., Xue-J. C., Zhuo C., Bao-A S., Pinaki S B., Song Y., Lin-H J., Wei X., De-Y H., Song Z.,(2008) Synthesis and Antiviral Activities of Pyrazole Derivatives Containing an Oxime Moiety. Journal of Agricultural and Food Chemistry, 56, 10160–10167. DOI: 10.1021/jf802489e
11. Pasin J.S.M., Ferreria A. P. O., Saraiva, A. L. L., Ratzlaff V., Andrighetto R., Machado P., Marchesam S., Zanette R. A., Martins M. A. P.,(2010) Antipyretic and antioxidant activities of 5-trifluoromethyl-4,5-dihydro-1H-pyrazoles in rats", Brazilian Journal of Medical and Biological Research., 43, 1193-1202. http://dx.doi.org/10.1590/S0100-879X2010007500139
12. Balbi A., Anzaldi M., Maccio C., Aiello C., Mazzei M., Gangemi R., (2011) Synthesis and biological evaluation of novel pyrazole derivatives with anticancer activity. European Journal of Medicinal Chemistry, 46, 5293-5309. http://dx.doi.org/10.1016/j.ejmech.2011.08.014
13. Ailwadi S., Yadav J. M., Pathak D., (2011) Synthesis and characterization of some substituted pyrazoles as analgesics and anti-inflammatory agents. Der Pharma Chemica. 3, 215-222.
14. Abdel-A. M., El-D. A., Abuo-R. G., Hassan A. A, (2009) Synthesis of novel pyrazole derivatives and evaluation of their antidepressant and anticonvulsant activities. European Journal of Medicinal Chemistry, 44, 3480–3487. http://dx.doi.org/10.1016/j.ejmech.2009.01.032
15. Rundles R.W, Wyngaarden J.B., (1969) Drugs and uric acid. Annual Review of Pharmacology, 9, 345-362.
16. Chung W.H., Wang C.W., Dao R.L., (2016). Severe cutaneous adverse drug reactions. The Journal of dermatology. 43 (7): 758–66. doi:10.1111/1346-8138.13430
17. Song J. U., Choi S. P., Kim T. H., Jung C.K., Lee J.Y., Jung S.H., Kim G.T., (2015) Design and synthesis of novel 2-(indol-5-yl)thiazole derivatives as xanthine oxidase inhibitor. Bioorganic & Medicinal Chemistry Letters, 25(6), 1254-1258. http://dx.doi.org/10.1016/j.bmcl.2015.01.055
18. Shi A., Wang D., Wang H., Wu Y., Tian H., Guan Q., Bao K., Zhang W., (2016) Synthesis and bio-evaluation of 2-phenyl-5-methyl-2H-1,2,3-triazole-4-carboxylic acid/carbohydrazide derivatives as potent xanthine oxidase inhibitors. RSC Advances, 6(115), 114879-114888. DOI: 10.1039/C6RA24651F
19. Noro T., Ehara M., Ueno A., (1990) Study of enzyme inhibitory activities by dipyridamole. Chemical & Pharmaceutical Bulletin, 38(5), 1403-1404 doi.org/10.1248/cpb.38.1403.
20. Ghag S.P., Kamath C.R., Dave M.A., Martin A.M., (2009) Synthesis and antimicrobial activity of 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carboxylic acid hydrazide and their Schiff's bases, Journal of Chemtracks, 11 (1),87-92.