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Synthesis of carboxamide and sulfonamide bearing novel pyrazolopyridones

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Abstract

The reaction of pyridones with hydrazine hydrate to furnished pyrazolopyridones 1a-l followed by reaction with p-Toluenesulfonyl chloride in basic condition affords 2a-l in high yields with short reaction time. The pyridone derivatives were prepared by the reaction of ketene dithioacetals (KDTA) with cyanoacetamide usingsodium isopropoxide as an effective base. The reactions were carried out with range of solvent and found i-Propyl alcohol as suitable solvent. We have demonstrated the process of highly functionalized pyrazolopyridones in high yields.

Keywords: Highly functionalized pyrazolopyridone, Sulfonamide and carboxamide, Ketene dithioacetal, Excellent yield.

Introduction

Pyrazole derivatives have extensive interest due to the wide diversity of their pharmacological actions. Reports indicate that numerous compounds having pyrazole moiety; pharmacological drugs, natural products, pesticides and dyes are published during the last decade. In addition, different insights into the properties such as conformations, tautomerisms, pyrolysis and decomposition reactions of pyrazoles are studied[1]. The word pyrazole was given to this class of compounds by German Chemist Knorr Ludwig in 1883[2]. Pyrazole was first synthesized by German chemist Pechmann Hans Von in 1898 by using acetylene and diazomethane[3].

Fused heterocycles have attracted important consideration from the scientific peoples due to their significance in medicinal chemistry. Fused heterocycles often can be observed in number of biologically active small compounds, and in actual, benzofused heterocycles attached to different heterocyclic moiety; pyridines, pyrimidines, isxoazoles and pyrazoles have been used as vital pharmacophores[4]. As depicted in Figure-1, sildenafil citrate (1)[5] a block buster drug and a effective antitumormolecule (2)[6], comprise she terocycles attached with privileged heterobiaryls as primary skeletons. Compound-3 is useful to stimulates soluble guanylatecyclase and prompts vasodilation, comprises the pyrazolopyridine heterocycle[7]. Moreover, pyrazolopyridine (4) have been stated as potent inhibitors of glycogen synthase kinase-3[8]. These case studies demonstrated the significance of fused pyrazolopyridones as main pharmacophores in biologically active small molecules.

Materials and methods

The solvents and chemicals were analytical grade and purchased from Loba and Himedia. 0.2-mm Silica gel coated plates was used for TLC. DMSO was used as solvent for ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectra on a Bruker AVANCE II spectrometer. Mass spectra were determined using an Agilent technology GCMS5977A. IR spectroscopic study was performed using Bruker alpha FTIR. Analab-μ Thermocal 10 was used to measure the Melting points of compounds.

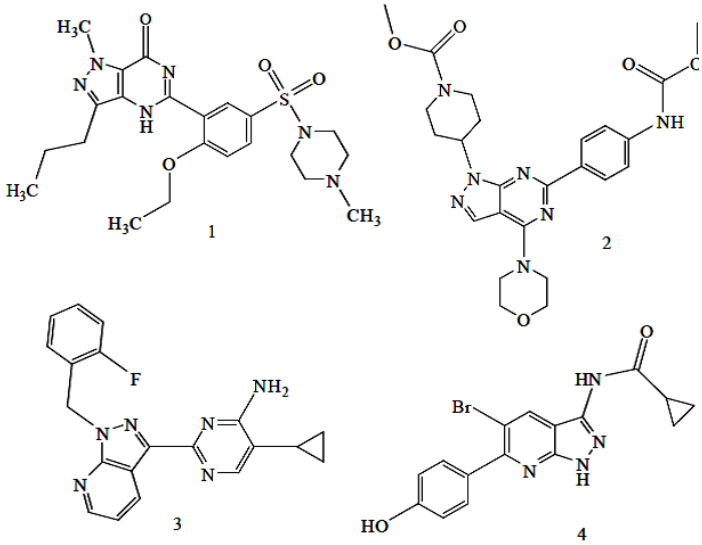


Figure-1: Biologically active pyrazolopyridones.

General process for preparation of substituted Ketene Dithioacetals: To the stirred solution of DMF and K_2CO_3 (2.2 equivalent) was 3-oxo-*N*-(aryl) butanamide compound (0.015mole) (1equivalent) and stirred it for about 30 min at room temperature. Then add solution of carbon disulfide in DMF with stirring in 25-30 min time duration at 0-5^{0}C temperature. After completion of the addition orange colored salt was obtained. After string for 30 min at rt. Then dimethyl sulfate in DMF (1.1) was added during 30 min at 0-5^{0}C and reaction mixture was stirred for 10-12 hr at rt. After completion,

mixture was poured into crushed ice slowly with continuous stirring so the separated ppt of ketene dithioacetal was obtained. Filtered of the product and washed with cold water then dried it. The product was used for next reaction without any purification.

General process for preparation of substituted Pyridones: Cyanoacetamide (5mmol) and sodium isopropoxide (5mmol) was added in IPA and stirred for 10 min. Then the solution of ketene dithioacetals (5mmol) was added along with isopropyl alcohol during period of 10-15 min with stirring. The reaction mixture was refluxed for 4-5 hr. After completion, the solvent was removed under pressure and the resultant crude was treated with dil. Hydrochloric acid solution. The separated product was filtered, washed with cold water and dried at room temperature to furnish desired solids.

General process for preparation of substituted Pyrazolopyridones: In a RBF, substituted Pyridones (5 mmol) and hydrazine hydrate (10mmol) were added in to solvent and refluxed on water bath for appropriate time. After completion, the reaction was poured into ice and separated solid product was filtered off then washed with water and dried at room temperature to furnished desire products.

General process for preparation of Pyrazolopyridones containing phenyl sulfonamide group (**2a-l**): The mixture of substituted pyrazolopyridones derivative and *p*-toluene sulfonyl chloride in pyridine was stirred for 24 hr at room temperature. The reaction was being monitored by TLC. The reaction mixture was then poured in to ice to furnished product 2a-l. Filter the separated product, wash with access water to remove the pyridine and dry at room temperature for moisture free product.

Analytical Data of *N*-(4-bromophenyl)-5-isopropyl-3-(4-methylphenylsulfonamido)-7-oxo-6,7-dihydro-1*H*-pyrazolo [3,4-c] pyridine-4-carboxamide: White solid; IR: 3483, 1696, 1665, 1604, 1395, 1172, 1072, 1012,823, 738, 469. ^{1}H NMRδ ppm: 1.19 (s, 6H, 2-CH_3); 2.40 (m, 1H, -CH); 2.51 (s, 3H, CH_3); 7.32-7.90 (m, 8H, Ar-H); 10.44(s, 1H, -CONH); 11.45(s, 1H, -NH-SO_2); 12.27(s, 1H, -NH); 12.84(s, 1H, - NH). ^{13}C NMR: 162.99, 160.7, 153.92, 151.17, 150.6, 145.46, 138.47, 133.30, 130.4, 127.6, 121.54, 115.03, 102.77, 94.04, 29.35, 21.17, 20.26, 19.76.

Results and discussion

The pyrazolopyridine and pyrazolopyrimidine derivatives displays broad range of pharmacological activities and have remarkable chemical and biological importance. As we discussed, the excellent pharmacological activity of pyrazolopyridone derivatives encouraged us to design and prepare some novel pyrazolopyridone derivatives. In literature, several approaches have been reported for the preparation of pyrazolopyridones. Nevertheless, the present process has several disadvantages, such as; low yield, extrareaction time, isolation of product, purification, byproduct formation. In contrast, various KDTA worked as flexible synthon in organic reaction for the construction of various heterocyclic compounds[9]. In our efforts to discover novel heterocycles using KDTA,[10-11] we observed that they are useful synthetic equivalents for preparation of pyrazolopyridones.

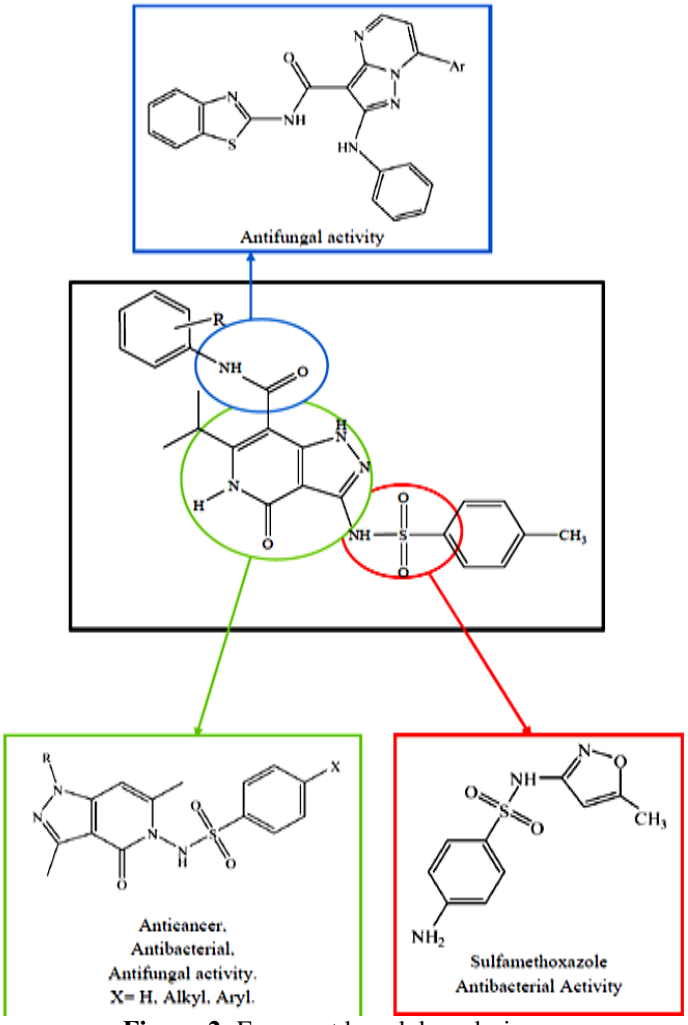
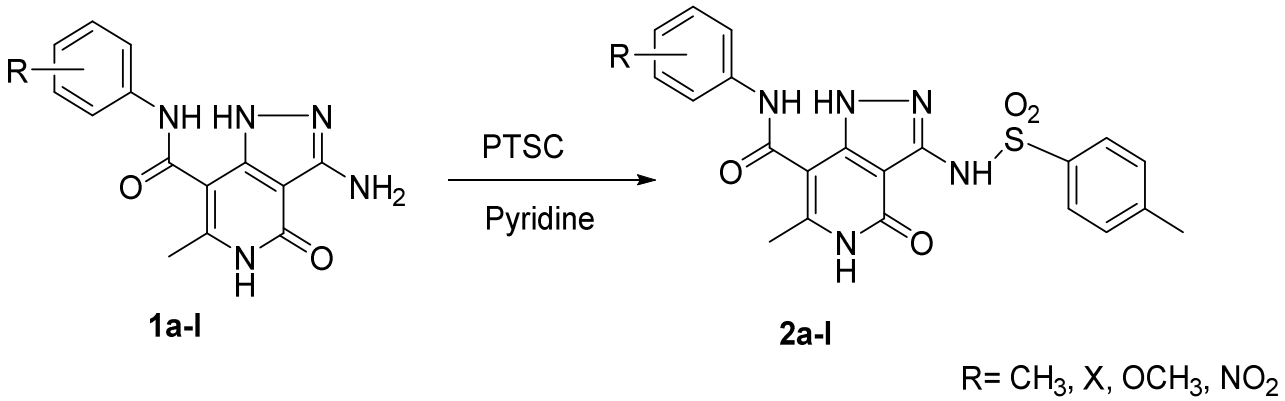


Figure-2: Fragment based drug design.

Fragment based structure activity relation encouraged us to synthesize a single compound having pyrazolopyridone moiety bearing sulfonamide and carboxamide substituents[12-13]. Fragment based drug design is shown in Figure-2.

Thus, to prepare desired pyrazolopyridones, the reaction of various KDTA with cyanoacetamide using base in IPA was performed to yield pyridones. Which were then reacted with hydrazine hydrate in isopropyl alcohol, then, to introduce the sulfonamide group the pyrazolopyridone derivatives were reacted with *p*-Toluenesulfonyl chloride to afford sulfonamide pyrazolopyridone derivatives. The synthesized compounds were characterized by IR, Mass, ^{1}H NMR, ^{13}C NMR spectroscopy and elemental analysis.

Initially, the pyrazolopyridone derivatives were synthesized by the reaction of hydrazine hydrate with pyridone derivatives using isopropyl alcohol as solvent in good to high yield with short reaction time. The resulting substituted pyrazolopyridones derivatives were reacts with *p*-Toluenesulfonyl chloride in pyridine as solvent afforded substituted pyrazolopyridones phenyl sulfonamide derivatives (2a-l) in excellent yield with long reaction time. The physical data of all synthesized derivatives 2a-l are given in Table-1.



Scheme-1: Synthesis of sulfonamide and carboxamide functionalizedpyrazolopyridones.

Table-1: Physical data of compounds 2a-l.

Entry	R	%Yield	Melting Range
2a	H	86	242-244 ^{0}C
2b	4-Br	76	229-231 ^{0}C
2c	4-NO_2	89	168-170 ^{0}C
2d	4-OCH_3	71	261-263 ^{0}C
2e	3-NO_2	71	172-174 ^{0}C
2f	3-OCH_3	71	252-254^{0}C
2g	4-F	89	212-214^{0}C
2h	2-OCH_3	91	226-228^{0}C
2i	2-CH_3	93	198-199^{0}C
2j	4-Cl	95	265-267^{0}C
2k	4-Et	85	231-233^{0}C
2l	3-CH_3	87	204-206^{0}C

Conclusion

In conclusion, we have demonstrated the process of sulfonamide group bearing pyrazolopyridones with high yields. Pyridone derivatives were prepared by the reaction of functionalized KDTA with cyanoacetamide using sodium isopropoxide as base. Novel pyrazolopyrdiones were prepared in excellent yield by the reaction of pyridones with hydrazine hydrate. The reaction of pyrazolopyridones with *p*-Toluenesulfonyl chloride in pyridine was afforded the desired compounds with good to moderate yield. The synthesized compounds will be screened for their anti-HIV and anti-cancer activity and report in future.

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