ORIGINAL RESEARCH PAPER

Chemistry

SYNTHESIS OF SOME OF PHARMACEUTICALLY IMPORTANT PYRIMIDO ANNULATED ANALOGUES OF CARBAZOLO AND AZACARBAZOLO CONDENSED TRIAZINE INDOLE

KEY WORDS: carbazolo, azacarbazolo, triazine indole, pyrimido, enol, ether, oxoketene dithioacetal and IR, 1HNMR and MS

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ABSTRACT

This paper describes the synthesis of carbazole, azacarbazole condensed pyrimidine derivatives **(4.041a-h)** and **(4.042a-h)** by cyclocondensation of oxoketenedithioacetal **4.040a-d** with urea, thiourea, acetamidine hydrochloride and guanidine nitrate respectively . The structure of all the compounds have been established by elemental analysis, and spectral (IR, 1HNMR and Ms) data.

Introduction

The aim in the present paper was to explore further its feasibility in the synthesis of carbazolo and azacarbazolo condensed pyrimidine derivatives.

Pyrimidine and condensed pyrimidine derivatives continue to attract great interest due to wide variety of interesting biological and pharmacological properties associated with these molecules[1]. Pyrimidines play a vital role in many biological processes since this ring system is present in several vitamines, coenzymes, nucleic acids etc. Synthetic members of these groups are also important as chemotherapeutic agents. The pyrimidine nucleus also occurs in a considerable number of natural products of vital importance to living organisms[2]. As a structural component of key biomolecules, the pyrimidine moiety is widely incorporated in the design of privileged structures.

Based on the precedence in the literature on the pharmacological activity of pyrimidines it was assumed that their incorporation on to the carbazole and azacarbazole molecule could produce interesting series of carbazolo/azacarbazolo fused pyrimidine derivatives with enhanced biological activities.

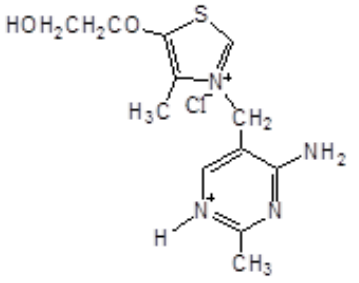
Though hydroxy, mercapto, amino and methyl pyrimidines are relatively little studied heterocyclic systems, but these are of interest in the context of drug development. These pyrimidines are important as significant number of compounds of this class have been used in synthetic, analytical and medicinal chemistry.

Pyrimidine nucleus has been the subject of substantial attention of synthetic and medicinal chemists because of the importance of the pyrimidine fused heterocyclic ring systems in many biological processes.[3,4]

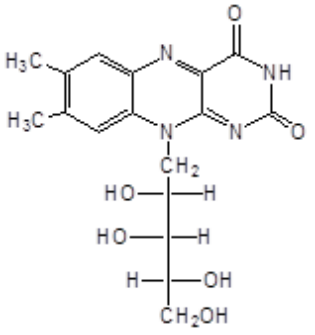
Pyrimidines are particularly interesting targets, for the synthesis of novel fused heterocycles due to their structural diversity and importance in the development of broad range of therapeutics. Five and six membered heterocyclic compounds containing one or two heteroatom fused to pyrimidine ring in a linear fashion are found in natural products as well as in the synthetic compounds of biological interest and are endowed with a distinguished history extending from the days of their discovery as important constituents of nucleic acids to their current use in the chemotherapy of AIDS.

Pyrimidine derivatives are also reported to possess antibacterial, antimicrobial, antifungal, anticancer and anticonvulsant activities1-3. The presence of pyrimidine nucleus in DNA and RNA, renders them to manifest their diverse biological acivities.

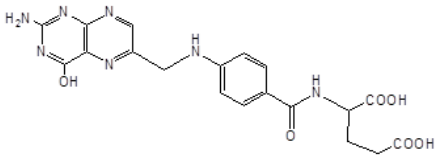
The pyrimidine ring is found in vitamins like thiamine **(4.001)**, riboflavin **(4.002)** and folic acid5 **(4.003). (Fig:4.1).**



4.001



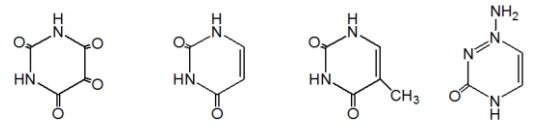
4.002



4.003

Fig:4.1

Alloxan **(4.004)** is known for its diabetogenic action in a number of animals6. Uracil **(4.005),** thymine **(4.006)** and cytosine **(4.007)** are the three important constituents of nucleic acids **(fig:4.2).**

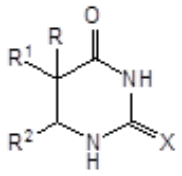


4.004 **4.005** **4.006** **4.007**

Fig:4.2

Drugs for hyperthyroidism

2-Thiouracil **(4.008a)** and its alkyl analogue, thiobarbital **(4.008c)** are effective drugs against hyperthyroidism. Propylthiouracil **(4.008b)** is used as a drug for hyperthyroidism with less side effects7 (fig:4.3).



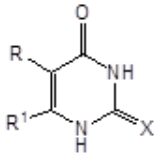
4.008

4.008a, R=R_1=R_2=H, X=S;
4.008b, R=R_1=H, R_2=C_3H_7, X=S;
4.008c, R=R_1=C_2H_5, R_2=O, X=S;

Fig:4.3

Antineoplastic and anticancer agents

There are a large number of pyrimidine-based antimetabolites which are useful as antineoplastic and anticancer agents. They are usually structurally related to the endogenous substrates, that they antagonize. The structural modification may be on the pyrimidine ring or on the pendant sugar groups. One of the early metabolites prepared was 5-fluorouracil8 (5-FU, **4.009a)**, a pyrimidine derivative. 5-Thiouracil **(4.009b)** also exhibits some useful antineoplastic activities **(fig:4.3).**

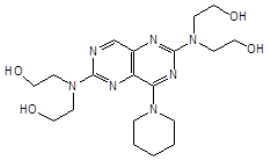


4.009

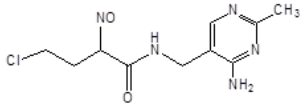
4.009a,X=O,R=F.R[1]=H.
4.009b, X=O,R=SH.R[1]=H.

Fig:4.3

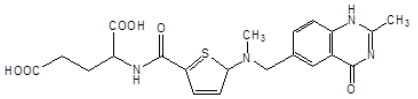
Many more have been included in this list in recent times, like mopidamol **(4.010)**, nimustine **(4.011)**, reltitrexed **(4.012) (fig:4.4)** and trimetrixater9 **(4.013)** etc. **(fig:4.5).**



4.010

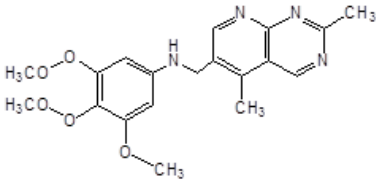


4.011



4.012

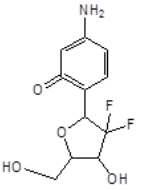
Fig:4.4



4.013

Fig:4.5

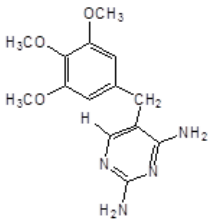
Gemcitabine **(4.014),** a pyrimidine antimetabolite **(fig:4.6)**, shows excellent antitumour activity against solid tumours10.



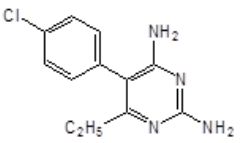
4.014

Fig:4.6Antifolates, antibacterials and antiprotozoals

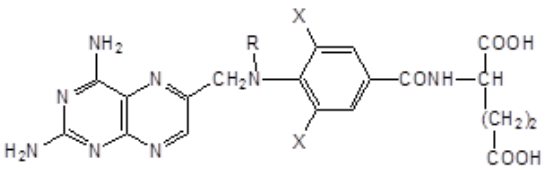
In 1948, Hitchings made an important observation that a large number of 2,4-diaminopyrimidines and some 2-amino 4-hydroxypyrimidines are antagonists of folic acid. Since then, a large number of 2,4-diaminopyrimidines have been synthesized as antifolates. It was eventually proved that these pyrimidines are inhibitors of the enzyme dihydrofolate reductase (DHFR)[11]. Notable amongst the 2,4-diaminopyrimidine drugs are pyrimethamine **(4.015)**, a selective inhibitor of the DHFR of malarial plasmodia; trimethoprim **(4.016),** an antibacterial drug which selectively inhibits bacterial DHFR and most importantly, the very potent but non selective DHFR inhibitors, methotrexate **(4.017a)** and aminopterin **(4.017b)**, both used in cancer chemotherapy[12]. 3',5'-Dichloromethotrexate **(4.017c)**, has recently been introduced for anticancer therapy[13]. Brodimoprim (**4.018)** is also found to be an effective antibacterial compound[14] **(fig:4.7)**.



4.015

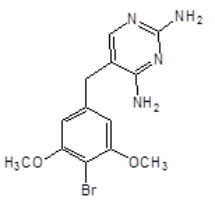


4.016



4.017

4.017a, R=CH_3, X=H
4.017b, R=X=H
4.017c, R=CH^3, X=Cl



4.018
Fig:4.1.3

Experimental

1. Melting points are determined in open glass capillaries and are uncorrected.
2. The purity of the compounds were checked by TLC on silica gel (G) plates.
3. IR spectra were recorded on CE (SHIMADZU) FTIR-8400S
4. 1H NMR spectra were recorded on medel AC-300F (Brucker) using CDCl3 /DMSO-d6 as solvent and TMS as an internal reference.Chemical shifts are expressed in ppm.
5. Before analysis all samples were dried for one hour under reduced pressure.
6. Physical and spectral data for all the compounds are given in table 4.1 and 4.2

Preparation of of 6,7- dihydro-2H-pyrrolo [2,3e] [1,2,4] triazin -3 (5H) –one- 1H- indol -5,6 –dihydro -4- (methyl thio) quinazoline -2-ol. (4.041a)

To a mixture of urea (1.0g 0.18mole) and sodium ethoxide (0.003) in ethanol was added appropriate ketene-S,S-acetal **4.040a** (1.0g 0.02mole) and the reaction mixture was refluxed for 14h. The solvent was removed by distillation and the residue was treated with glacial acetic acid (7-10ml) just enough to dissolve sodium salt of pyrimidine and refluxed for 15min. The reaction mixture was poured on crushed ice and the precipitate obtained was purified by crystallization in ethanol to give **4.041a** 0.5 gm (yield:65%) m.p.270-2720C. Similarly compound 4.041c and **4.041e, 4.041g** were obtained from **4.040a**-d respectively. Melting point and yield of these compounds are given in table **4.1.**

Preparation of 6,7- dihydro-2H-pyrrolo [2,3e] [1,2,4] triazin -3 (5H) –one -1H indol 5,6 –dihydro -4- (methyl thio) quinazoline -2-thiol (4.041b)

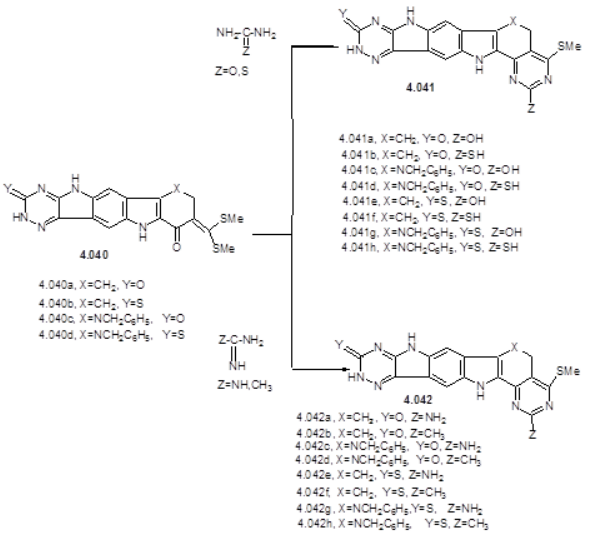
To a mixture of thiourea (1.0g 0.18mole) and sodium ethoxide (0.003) in ethanol was added appropriate ketene-S,S-acetal **4.040a** (1.0g 0.02mole) and the reaction mixture was refluxed for 14hs. The solvent was removed by distillation and the residue was treated with glacial acetic acid (7-10ml) just enough to dissolve sodium salt of pyrimidine and refluxed for 15min. The reaction mixture was poured on crushed ice and the precipitate obtained was purified by crystallization in ethanol to give **4.041b** 0.43gm (yield: 68%) m.p. 285-2870C. Similarly compound **4.041d** and **4.041f, 4.041h** were obtained from **4.040a-d** respectively. Melting point and yield of these compounds are given in table **4.1**.

Preparation of 6,7- dihydro-2H-pyrrolo [2,3e] [1,2,4] triazin -3 (5H) –one -1H indol 5,6 –dihydro -4- (methyl thio) quinazoline -2-amine. (4.042a)

To a solution of sodium ethoxide (1.0g 0.02 mole) in ethanol, guanidine nitrate (0.01 mole) was added and the reaction mixture was stirred for 10-15min. Oxoketene dithioacetals **4.040** was added and refluxed for 2hs. And the reaction mixture was poured into ice cold water. The solid separated was filtered, washed with diethyl ether and dried. Recrystallization from ethanol gave the analytically pure product **4.042a** 0.65 gm (yield:65%) m.p. 320-3220C product as colourless crystals. Similarly compound **4.042c, 4.042e**, and **4.042g** were obtained from **4.040a-d** respectively. Melting point and yield of these compounds are given in table **4.1**.

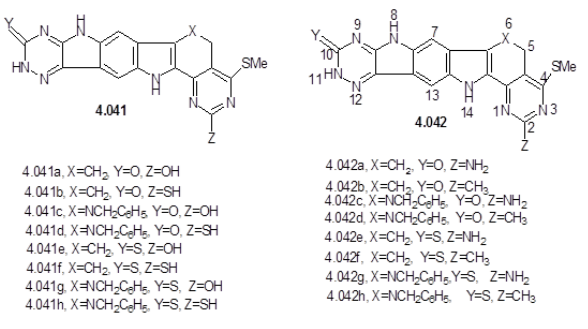
Preparation of 6,7- dihydro-2H-pyrrolo [2,3e] [1,2,4] triazin -3 (5H) –one -1H indol -5,6 –dihydro -2-methyl -4- (methyl thio) quinazoline. (4.042b)

To a solution of sodium ethoxide (1.0g 0.02 mole) in ethanol, acetamidine hydrochloride (1.0g 0.01 mole) was added and the reaction mixture was stirred for 10-15min. Oxoketene dithioacetals **4.040** was added and refluxed for 2hs. And the reaction mixture was poured into ice cold water. The solid separated was filtered, washed with diethyl ether and dried. Recrystallization from ethanol gave the analytically pure product **4.042b** 0.61gm (yield:60%) 300-3020C as colourless crystals. Similarly compound **4.042d** and **4.042f,4.042h** were obtained from **4.040a-d** respectively. Melting point and yield of these compounds are given in table **4.1.**



4.3 Result and discussion

In the present work, the synthesis of pyrimidine derivatives was carried out by the cyclocondensation of oxoketene dithioacetals with urea, thiourea, acetamidine and guanidine respectively. Synthesis of oxoketenedithioacetals **4.040a-d** was already described in chapter 2. When ketene S,S-acetals **4.040a-d** were reacted with urea, thiourea, acetamidine, guanidine in the presence of sodium ethoxide in boiling ethanol, the corresponding pyrimidine derivatives **4.041a-h** and **4.042a-**h were obtained in good yield (scheme 4.7). Reaction of acetals 4.040a-d with urea and thiourea in the presence of sodium ethoxide in ethanol was carried out with smooth displacement of the SMe group to afford the corresponding derivatives **4.041a, 4.041c, 4.041e, 4.041g and 4.041b, 4.041d, 4.041f , 4.041h** respectively. Similarly compounds **4.042a, 4.042c, 4.042e, 4.042g** and **4.042b, 4.042d, 4.042f, 4.042h** were obtained on reaction of 4.040a-d with guanidine nitrate and acetamidine hydrochloride respectively in the presence of sodium methoxide in methanol.



Conclusion

In conclusion, an efficient methodology for the synthesis of pyrimido condensed oxocarbazoles and their one-pot conversion to corresponding carbazolo and azacarbazolo fused triazine indole derivatives was doveloped. Hetrocyclic scaffolds bearing these structures have been widely studied because of their impressive

pharmaceutical activities. It was, therefore, reasoned that the presence of pyrimidine, carbazole or azacarbazole in tendem with the same molecular framework could produce the novel hetrocyclic scaffolds with interesting biological activities.

4.7 References

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