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SYNTHESIS OF BIOLOGICAL ACTIVE THIAZOLO-QUINAZOLINES

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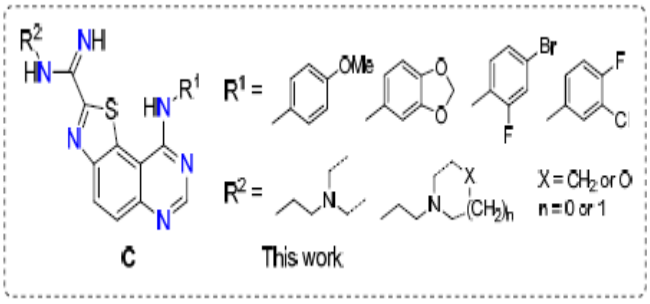
Introduction

Thiazolo-quinazolinones are classes of fused heterocycles that are of considerable interest because of the diverse range of their biological properties [1]. Many substituted quinazoline and quinazolinone derivatives possess a wide range of bioactivities such as antimalarial, anticancer, antimicrobial, antifungal, antiviral, antiprotozoan, anti-inflammatory, diuretic, muscle relaxant, antitubercular, antidepressant, anticonvulsant, acaricidal, weedicide, and many other biological activities. Quinazoline and quinazolinone compounds are also used in preparation of various functional materials for synthetic chemistry and also present in various drugs molecules (Figure 1). This review is an attempt to expand the huge potentiality and focused on the various biological activities of quinazolines and quinazolinones [2].



Synthesis

Thiazolo-quinazolines - substituted in position 4 of the pyrimidine ring (which corresponds to position 9 of the tricyclic compound) by an aromatic amine. The retrosynthetic pathway depicted in Scheme 1 was directly inspired by our previous work on the synthesis of various thiazoloquinazoline isomers[4,5] and on general access to pyrimidine-condensed heterocyclic compounds [6].It suggested introducing the thiazole ring via a copper(I)-mediated cyclization of *ortho*-brominated *N*-arylimino-1,2,3-dithiazoles intermediates. The latter would be isolated after condensation of 4,5-dichloro-1,2,3-dithiazolium chloride (Appel salt) [7]with a key *N*2-protected brominated aminoanthranilonitrile. The synthesis of the final pyrimidinic structures was envisioned via a microwave-assisted thermal-sensitive Dimroth rearrangement.[8]

In the present work, the synthetic sequence is easily upscalable and 10 g of 2-amino-5-nitrobenzonitrile led to 2 g of **3** in an average 23% yield. This new compound **3** can be considered as a molecular platform that can be employed in new areas of investigation and prove its utility for the synthesis of innovative molecular systems with potent biological applications. Indeed, the versatile carbonitrile function in position 2 of the thiazole ring may allow the synthesis of various amidine, imidazoline and imidate derivatives. On the other side the 2-aminobenzonitrile moiety offers a large panel of possibilities for extension of the aromatic structure with a heterocyclic core such as a pyrimidine.

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Experimental Section

General Information

All reactions were carried out under inert atmosphere and monitored by thin-layer chromatography (TLC) with silica gel 60 aluminum plates . Visualization was performed with a UV lamb at 250 and 310 nm. Purifications were carried out on an Armen Instrument Spot 2 Flash System equipped with a dual UV-Vis spectrophotometer (200–600 nm), a fraction collector (192 tubes), a dual piston pump (1 to 250 mL/min, Pmax = 50 bar/725 psi) allowing quaternary gradients and an additional inlet for air purge. Samples can be injected in liquid or solid mode. Purification was edited and monitored on an integrated panel PC with a touch screen controlled by Armen Glider Flash v3.1d software [28]. Biotage SNAP flash chromatography cartridges (KP-Sil, normal phase, 10 to 340 g) were used for the purification process. Melting points of solid compounds were measured on a WME Köfler hot-stage with a precision of +/−2 °C and are uncorrected. IR spectra were recorded on a PerkinElmer Spectrum 100 Series FT-IR spectrometer. Liquids and solids were applied on the Single Reflection Attenuated Total Reflectance (ATR) Accessories. Absorption bands are given in cm−1. 1H/19F/13C-NMR spectra were recorded on a Bruker DXP 300 spectrometer at 300, 282 and 75 MHz respectively. Abbreviations used for peak multiplicities are s: singlet, d: doublet, t: triplet, q: quadruplet and m: multiplet. Coupling constants *J* are in Hz and chemical shifts are given in ppm and calibrated with DMSO-*d*6 or CDCl3 (residual solvent signals). Mass spectra analysis was performed by the Mass Spectrometry Laboratory of the University of Rouen. Mass spectra (EI) were recorded with a Waters LCP 1er XR spectrometer.

N-(Benzo[d][1,3]dioxol-5-yl)-6-nitroquinazoline (**3**). A mixture of N'-(2-cyano-4-

nitrophenyl)-*N*,*N*-dimethylformamidine (**2**, 1.0 g, 4.58 mmol) and 3,4-(methylenedioxy)aniline in acetic acid was heated at 120 °C under microwaves (600 W). On completion of the reaction was cooled to ambient temperature. The separated solid was filtered and washed with ether to obtain the expected compound **3b** (70%) as a brown solid; mp > 266 °C. 1H-NMR (DMSO-*d*6) δ 10.5 (s, 1H, NH), 9.59 (d, 1H, *J* = 2.1 Hz), 8.64 (s, 1H), 8.55 (dd, 1H, *J*1 = 2.1 Hz, *J*2 = 9.0 Hz), 7.89 (d, 1H, *J* = 9.0 Hz), 7.55 (s, 1H), 7.21 (m, 1H), 6.90 (d, 1H, *J* = 9.0 Hz), 5.80 (s, 2H); 13C-NMR (DMSO-*d*6) δ 159.1, 156.9, 151.9, 145.1, 144.8, 144.0, 132.2, 129.1, 126.1, 120.7, 115.8, 114.8, 107.9, 105.9, 100.9.

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