Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
ELSEVIER
Tetrahedron 62 (2006) 9787–9826

Tetrahedron report number 771

The chemistry of recently isolated naturally occurring quinazolinone alkaloids☆

Santosh B. Mhaske* and Narshinha P. Argade*

Division of Organic Chemistry (Synthesis), National Chemical Laboratory, Pune 411 008, India

Received 25 July 2006
Available online 22 August 2006

Abstract—The present review portrays a concise account of the isolation, bioactivity, and synthesis of bioactive quinazolinone-based natural products for the period 1983–2005 and the recent developments in the area of complex quinazolinone natural products with a special emphasis on new synthetic routes and strategies.

Contents

☆ NCL Communication No. 6694.

Keywords: Natural quinazolinones; Isolation; Bioactivity; Synthesis; Concise account; 1983–2005.

Abbreviations: AIBN, 2,2′-azobisisobutyronitrile; Bn, benzyl; Boc, *tert*-butoxycarbonyl; BOP, benzotriazol-1-yloxytris(dimethylamino)-phosphoniumhexafluorophosphate; CAN, ceric ammonium nitrate; Cbz, carbobenzyloxy; CCK, cholecystokinin; COX-2, cyclooxygenase-2; CyH, cyclohexane; DBP, dibenzoyl peroxide; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DCC, 1,3-dicyclohexylcarbodiimide; DCM, dichloromethane; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DEAD, diethyl azodicarboxylate; DMA, dimethyl acetamide; DMAP, 4-(dimethylamino)pyridine; DMF, dimethylformamide; DMSO, dimethyl sulfoxide; DPPF, diphenylphosphinoferrocene; $Dy(OTf)_3$, dysprosium trifluoromethanesulfonate; EDAC, *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride; EDC, *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide; Fmoc, 9-fluorenylmethoxycarbonyl; IC, inhibitory concentration; KHMDS, potassium hexamethyldisilazide; LAH, lithium aluminum hydride; LDA, lithium diisopropylamide; Lipase PS, lipase from *Burkholderia cepacia*; *m*-CPBA, *meta*-chloroperbenzoic acid; MDR, multiple drug resistance; MF, molecular formula; MS, molecular sieves; MW, microwave; NBS, *N*-bromosuccinimide; NMP, *N*-methylpyrrolidinone; PCC, pyridinium chlorochromate; PCy_3, tricyclohexylphosphine; $Pd_2(dba)_3$, tris(dibenzylideneacetone)dipalladium; PPA, polyphosphoric acid; PPTS, pyridinium *p*-toluenesulfonate; *p*-TsCl, *p*-toluenesulfonyl chloride; *p*-TsOH, *p*-toluenesulfonic acid; Py, pyridine; TBAF, tetrabutylammonium fluoride; TBDMS, *tert*-butyldimethylsilyl; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TEA, triethylamine; TFA, trifluoroacetic acid; TFAA, trifluroacetic anhydride; THF, tetrahydrofuran; TMSCl, trimethylchlorosilane; TMSI, trimethyliodosilane.

* Corresponding authors. Tel.: +91 20 25902333; fax: +91 20 25902624; e-mail: np.argade@ncl.res.in

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.07.098

1. Introduction

Quinazolinone (Fig. 1) is a building block for approximately 150 naturally occurring alkaloids isolated to date from a number of families of the plant kingdom, from animals and from microorganisms. The first quinazolinone was synthesized[1] in the late 1860s from anthranilic acid and cyanogen to give 2-cyanoquinazolinone (**1**, Fig. 2). Interest in the medicinal chemistry of quinazolinone derivatives was stimulated in the early 1950s with the elucidation of a quinazolinone alkaloid, 3-[β-keto-γ-(3-hydroxy-2-piperidyl)-propyl]-4-quinazolone [febrifugine[2] (**2**), Fig. 2], from an Asian plant *Dichroa febrifuga*, which is an ingredient of a traditional Chinese herbal remedy, effective against malaria.

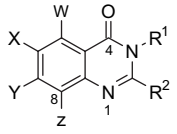

Figure 1. Quinazolinone basic structure.

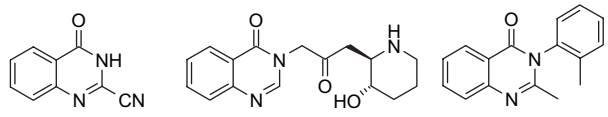

Figure 2. Synthetic and natural quinazolinones.

In a quest to find additional potential quinazolinone-based drugs, various substituted quinazolinones have been synthesized, which led to the synthesis of the derivative, 2-methyl-3-*o*-tolyl-4-(3*H*)-quinazolinone [methaqualone (**3**), Fig. 2]. Methaqualone (**3**) was synthesized[3] for the first time in 1951 and it is the most well-known synthetic quinazolinone drug, famous for its sedative–hypnotic effects.[4] The introduction of methaqualone and its discovery as a hypnotic triggered the research activities toward the isolation, synthesis, and studies on the pharmacological properties of the quinazolinones and related compounds. Quinazolinones and their derivatives are now known to have a wide range of useful biological properties, such as hypnotic, sedative, analgesic, anti-convulsant, anti-tussive, anti-bacterial, anti-diabetic, anti-inflammatory, anti-tumor, and several others.[5,6] The chemistry of the quinazolinone alkaloids is well documented[5,6] in a number of comprehensive reviews and monographs and is continuously updated in *Natural Product Reports*.[7]

The review by Johne[6b] has covered the literature of all the quinazolinone natural products isolated up to the middle of 1983. After 1983, relatively few reviews have appeared on quinazolinones, which were very specific to either selected natural products[5,6i] or to general quinazolinone synthetic methods.[6g,h] Quinazolinone is an important pharmacophore and several new natural products have been isolated and synthesized during the past two decades. We, therefore feel that a complete literature review of all the quinazolinone natural products isolated after 1983 is necessary at this point in time. Accordingly, the present review portrays a concise account of the isolation, bioactivity, and synthesis of naturally occurring quinazolinone alkaloids isolated after the middle of 1983 up to 2005, pertaining strictly to the basic structure shown in Figure 1 and recent developments in the area of the complex quinazolinone natural products, with an emphasis on new synthetic routes and strategies. The chemistry of quinazolinone alkaloids is published in a broad range of scientific journals. We have tried, to the best of our ability, to assemble and present the information on natural quinazolinones in this report, but no pretension of completeness is claimed. In order to simplify and understand the chemistry of the naturally occurring quinazolinone alkaloids, these compounds have been divided into subclasses according to their structures. Each group contains information about the natural products in tabular form, incorporating their structure, name, molecular formula, species from which they were isolated, bioactivity, and references pertaining to synthesis. A table is followed by a discussion and illustration of the synthesis of the representative quinazolinone alkaloids from the list. In the last part, the biological activity of quinazolinones and their applications in clinical treatments have been discussed and this is followed by a final summary.

Quinazolinone derivatives are of interest because of their pharmacological properties,[6g,8] e.g., protein tyrosine kinase inhibitory, cholecystokinin inhibitory, anti-microbial, anti-convulsant, sedative, hypotensive, anti-depressant, anti-inflammatory, and anti-allergy properties. Some of these compounds also have interesting biological properties[8] such as anti-malarial activity, biofungicide, and diuretic properties. A literature survey has revealed that there are about 75 new quinazolinone-based natural products isolated under the present review period, and these were characterized by UV, IR, ^{1}H NMR, ^{13}C NMR, 2D NMR, and mass spectroscopic methods, together with X-ray crystallographic analysis data. In view of the importance of quinazolinones and their derivatives, many classical methods for their synthesis have been reported in the literature.[5,6g,h,8,9] The main synthetic routes to quinazolinone compounds utilize 2-aminobenzoic acid or its derivatives, 2-aminobenzamide, 2-aminobenzonitrile, isatoic anhydride, 2-carbomethoxyphenyl isocyanate, *N*-arylnitrilium salts, and 4*H*-3,1-benzoxazinones as suitable precursors. In the solid-phase synthesis field, lithium reagents and transition metals have been used for the preparation of these compounds.[5] Other important methods include coupling of *O*-methylbutyrolactam with anthranilic acid, cycloaddition of anthranilic acid iminoketene to methylbutyrolactam (via sulfonamide anhydride), reactions of anthranilic acid derivatives with a wide range of substrates including imidates and imino halides, the reaction of anthranilic acid and the appropriately substituted imidate in a facile one-pot procedure, and microwave-promoted reaction of anthranilic acid with amines and formic acid (or its *ortho* ester) and isatoic anhydride.[9]

All the important methods for the synthesis of the quinazolinone alkaloids are described in the following sections in detail. These alkaloids have been divided into six major categories according to their structural features and further subdivided depending on their substitution pattern.